OPEN ACCESS

University of Dundee

University of Dundee

Understanding causes of and developing effective interventions for schizophrenia and other psychoses

Perez, Jesus; Russo, Debra A.; Stochl, Jan; Shelley, Gillian F.; Crane, Carolyn M.; Painter, Michelle

Published in:
Programme Grants for Applied Research

DOI:
10.3310/pgfar04020

Publication date:
2016

Licence:
UK Government Non-Commercial Licence

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Discovery Research Portal

Citation for published version (APA):
Perez, J., Russo, D. A., Stochl, J., Shelley, G. F., Crane, C. M., Painter, M., Kirkbride, J. B., Croudace, T. J., & Jones, P. B. (2016). Understanding causes of and developing effective interventions for schizophrenia and other psychoses. *Programme Grants for Applied Research*, *4*(2), 1-184. https://doi.org/10.3310/pgfar04020

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying the publication in the public portal.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 05. May. 2023

PROGRAMME GRANTS FOR APPLIED RESEARCH

VOLUME 4 ISSUE 2 MARCH 2016
ISSN 2050-4322

Understanding causes of and developing effective interventions for schizophrenia and other psychoses

Jesus Perez, Debra A Russo, Jan Stochl, Gillian F Shelley, Carolyn M Crane, Michelle Painter, James B Kirkbride, Tim J Croudace and Peter B Jones

National Institute for Health Research

DOI 10.3310/pgfar04020

Understanding causes of and developing effective interventions for schizophrenia and other psychoses

Jesus Perez,[1,2,3] Debra A Russo,[1,2,3] Jan Stochl,[1,2,3] Gillian F Shelley,[1] Carolyn M Crane,[1,2] Michelle Painter,[1] James B Kirkbride,[3,4] Tim J Croudace[5] and Peter B Jones[1,2,3*]

[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[2]Department of Psychiatry, University of Cambridge, Cambridge, UK
[3]National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care, East of England, Cambridge, UK
[4]Division of Psychiatry, University College London, London, UK
[5]School of Nursing and Midwifery, University of Dundee, Dundee, UK

*Corresponding author

Declared competing interests of authors: none

Published March 2016
DOI: 10.3310/pgfar04020

This report should be referenced as follows:

Perez J, Russo DA, Stochl J, Shelley GF, Crane CM, Painter M, *et al*. Understanding causes of and developing effective interventions for schizophrenia and other psychoses. *Programme Grants Appl Res* 2016;**4**(2).

Programme Grants for Applied Research

ISSN 2050-4322 (Print)

ISSN 2050-4330 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full PGfAR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/pgfar. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Programme Grants for Applied Research* journal
Reports are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health Research (NIHR), was set up in 2006 to produce independent research findings that will have practical application for the benefit of patients and the NHS in the relatively near future. The Programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director.

The programme is a national response mode funding scheme that aims to provide evidence to improve health outcomes in England through promotion of health, prevention of ill health, and optimal disease management (including safety and quality), with particular emphasis on conditions causing significant disease burden.

For more information about the PGfAR programme please visit the website: http://www.nihr.ac.uk/funding/programme-grants-for-applied-research.htm

This report

The research reported in this issue of the journal was funded by PGfAR as project number RP-PG-0606-1335. The contractual start date was in August 2007. The final report began editorial review in April 2015 and was accepted for publication in December 2015. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, NETSCC, PGfAR or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the PGfAR programme or the Department of Health.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Programme Grants for Applied Research Editor-in-Chief

Professor Paul Little Professor of Primary Care Research, University of Southampton, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Professor Aileen Clarke Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson Director of NETSCC, HTA, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Professor Elaine McColl Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Health Sciences Research, Health and Wellbeing Research and Development Group, University of Winchester, UK

Professor John Norrie Health Services Research Unit, University of Aberdeen, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of members of the NIHR Journals Library Board:
www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk

Abstract

Understanding causes of and developing effective interventions for schizophrenia and other psychoses

Jesus Perez,[1,2,3] Debra A Russo,[1,2,3] Jan Stochl,[1,2,3] Gillian F Shelley,[1] Carolyn M Crane,[1,2] Michelle Painter,[1] James B Kirkbride,[3,4] Tim J Croudace[5] and Peter B Jones[1,2,3]*

[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[2]Department of Psychiatry, University of Cambridge, Cambridge, UK
[3]National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care, East of England, Cambridge, UK
[4]Division of Psychiatry, University College London, London, UK
[5]School of Nursing and Midwifery, University of Dundee, Dundee, UK

*Corresponding author pbj21@cam.ac.uk

Background: Early-intervention services (EISs) offer prompt and effective care to individuals with first-episode psychosis (FEP) and detect people at high risk (HR) of developing it.

Aims: We aimed to educate general practitioners about psychosis and guide their referrals to specialist care; investigate determinants of the transition of HR to FEP; and predict numbers of new cases to guide policy and service planning.

Incidence of psychosis in socially and ethnically diverse settings: We studied the incidence of new referrals for psychosis in a well-established EIS called CAMEO [see www.cameo.nhs.uk (accessed 18 January 2016)] and built on other epidemiological studies. The overall incidence of FEP was 45.1 per 100,000 person-years [95% confidence interval (CI) 40.8 to 49.9 per 100,000 person-years]. This was two to three times higher than the incidence predicated by the UK Department of Health. We found considerable psychosis morbidity in diverse, rural communities.

Development of a population-level prediction tool for the incidence of FEP: We developed and validated a population-level prediction tool, PsyMaptic, capable of accurately estimating the expected incidence of psychosis [see www.psymaptic.org/ (accessed 18 January 2016)].

The Liaison with Education and General practiceS (LEGS) trial to detect HR: We tested a theory-based intervention to improve detection and referral of HR individuals in a cluster randomised controlled trial involving primary care practices in Cambridgeshire and Peterborough. Consenting practices were randomly allocated to (1) low-intensity liaison with secondary care, a postal campaign to help with the identification and referral of individuals with early signs of psychosis, or (2) the high-intensity theory-based intervention, which, in addition to the postal campaign, included a specialist mental health professional to liaise with each practice. Practices that did not consent to be randomised included a practice-as-usual (PAU) group. The approaches were implemented over 2 years for each practice between April 2010 and October 2013. New referrals were stratified into those who met criteria for HR/FEP (together: psychosis true positives) and those who did not fulfil such criteria (false positives). The primary outcome was the number of HR referrals per practice. Referrals from PAU practices were also analysed. We quantified the cost-effectiveness of the interventions and PAU using the incremental cost per

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

additional true positive identified. Of 104 eligible practices, 54 consented to be randomised. Twenty-eight practices were randomised to low-intensity liaison and 26 practices were randomised to the high-intensity intervention. Two high-intensity practices withdrew. High-intensity practices referred more HR [incidence rate ratio (IRR) 2.2, 95% CI 0.9 to 5.1; $p = 0.08$], FEP (IRR 1.9, 95% CI 1.05 to 3.4; $p = 0.04$) and true-positive (IRR 2.0, 95% CI 1.1 to 3.6; $p = 0.02$) cases. High-intensity practices also referred more false-positive cases (IRR 2.6, 95% CI 1.3 to 5.0; $p = 0.005$); most (68%) of these were referred on to appropriate services. The total costs per true-positive referral in high-intensity practices were lower than those in low-intensity or PAU practices. Increasing the resources aimed at managing the primary–secondary care interface provided clinical and economic value.

The Prospective Analysis of At-risk mental states and Transitions into psycHosis (PAATH) study: We aimed to identify the proportion of individuals at HR who make the transition into FEP and to elucidate the common characteristics that can help identify them. Sixty help-seeking HR individuals aged 16–35 years were stratified into those who met the criteria for HR/FEP (true positives) according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) and those who did not (false positives). HR participants were followed up over 2 years using a comprehensive interview schedule. A random sample of 60 healthy volunteers (HVs) matched for age (16–35 years), sex and geographical area underwent the same battery of questionnaires. Only 5% of our HR sample transitioned to a structured clinical diagnosis of psychosis over 2 years. HR individuals had a higher prevalence of moderate or severe depression, anxiety and suicidality than HVs. In fact, psychometric analyses in other population samples indicate that psychotic experiences measure the severe end of a common mental distress factor, consistent with these results. HR individuals also experienced significantly more traumatic events than HVs, but equivalent distress. Almost half of HR individuals had at least one Schneiderian first-rank symptom traditionally considered indicative of schizophrenia and 21.6% had more than one. HR individuals had very poor global functioning and low quality of life.

Conclusions: This National Institute for Health Research programme developed our understanding of the social epidemiology of psychosis. A new theory-based intervention doubled the identification of HR and FEP in primary care and was cost-effective. The HR mental state has much in common with depression and anxiety; very few people transitioned to full psychosis over 2 years, in line with other recent evidence. This new understanding will help people at HR receive appropriate services focused on their current mental state.

Trial registration: The primary LEGS trial is registered as ISRCTN70185866 and UKCRN ID 7036. The PAATH study is registered as UKCRN ID 7798.

Funding: The National Institute for Health Research Programme Grants for Applied Research programme.

Contents

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of tables

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of figures

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of abbreviations

ÆSOP	Aetiology and Ethnicity in Schizophrenia and Other Psychoses
aOR	adjusted odds ratio
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory version II
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BRC	Biomedical Research Centre
CAARMS	Comprehensive Assessment of At-Risk Mental States
CAR	Client Assessment Register
CBT	cognitive–behavioural therapy
CI	confidence interval
CPFT	Cambridgeshire and Peterborough NHS Foundation Trust
cRCT	cluster randomised controlled trial
CRIS	Clinical Record Interactive Search
D-CRIS	Clinical Record Interactive Search (Collaboration Programme)
DUP	duration of untreated psychosis
DVD	digital versatile disc
EIS	early-intervention service
ELFEP	East London First-Episode Psychosis
EPRS	electronic patient record system
FEP	first-episode psychosis
fMRI	functional magnetic resonance imaging
FRS	first-rank symptom
GAF	Global Assessment of Functioning
GP	general practitioner
HoNOS	Health of the Nation Outcome Scales
HoNOS-PbR	Health of the Nation Outcome Scales – payment by results
HR	high risk
HV	healthy volunteer
IAPT	Improving Access to Psychological Therapies
ICD-10	*International Classification of Diseases*, 10th revision
IRR	incidence rate ratio
IT	information technology
LAD	local authority district
LEGS	Liaison with Education and General practiceS
MANSA	Manchester Short Assessment of Quality of Life
MINI	Mini-Neuropsychiatric Interview
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PAATH	Prospective Analysis of At-risk mental states and Transitions into psycHosis
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PAU	practice as usual
PBC	perceived behavioural control
PbR	payment by results
PCRN	Primary Care Research Network
PI	prediction interval
PPI	patient and public involvement
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
RLP	research and liaison practitioner
SD	standard deviation
SEPEA	Social Epidemiology of Psychoses in East Anglia

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

SLAM	South London and Maudsley	YBOCS	Yale–Brown Obsessive Compulsive Scale
THS	Trauma History Screen	YMRS	Young Mania Rating Scale
TPB	theory of planned behaviour		

Plain English summary

We studied first-episode psychotic disorders and at-risk mental states, also called high-risk mental states, which, when we began the programme, were considered precursors of psychotic illnesses.

We developed an enhanced new way to work with general practices and sixth-form colleges (the intervention) to help them identify and refer young people at high risk of developing psychosis. We then did an experiment, the Liaison with Education and General practiceS (LEGS) cluster randomised controlled trial, to test whether or not the new method led to more people at high risk being referred by general practitioners (GPs) to our early-intervention service called CAMEO. The intervention doubled GPs' identification and referral of young people with high-risk mental states as well as those with first-episode psychosis and other mental health problems. Economic modelling demonstrated that this way of working with GPs was economically beneficial for the NHS by reducing the costs of unrecognised mental illness. A parallel trial in sixth-form colleges is yet to report.

We followed 60 young people at high risk for 2 years in the Prospective Analysis of At-risk mental states and Transitions into psycHosis (PAATH) study. In only three young people (5%) did their mental state transition into a first-episode psychosis, fewer than initially expected but similar to results emerging from other studies. Most of the people at HR that we followed had significant depression and anxiety and many had suffered childhood trauma. Identifying this means that services can offer appropriate treatment and not just wait and see whether or not such individuals will develop a first-episode psychosis.

We showed that people from black and minority ethnic groups in rural areas as well as in cities have high mental health needs regarding first-episode psychosis. We developed the PsyMaptic tool to predict the numbers of young people who will require early-intervention services around the country.

The results of the LEGS trial and the PsyMaptic tool are now being used by NHS England to guide the allocation of mental health service funding.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Scientific summary

Background

Psychotic illnesses such as schizophrenia cause enormous disability and are expensive for sufferers and society. Developments in treatment interventions have been slow but mental health services have changed dramatically over the last decade.

A simple but radical idea concerns early-intervention services (EISs). In essence, EISs aim to identify people with psychosis promptly and treat them promptly. Anxiety, depression and short-lived individual psychotic features appear to put people at high risk (HR) of developing a full psychotic syndrome. Identifying and treating this HR phase in which people have an at-risk mental state for psychosis may improve outcomes.

Aims and intended outputs

We focused on people with first-episode psychosis (FEP) or mental states that put them at HR for FEP with the aim of identifying them early. One output was a method of educating general practitioners (GPs) and sixth-form colleges about psychosis and guiding their referral behaviour. We also aimed to investigate the nature and causes of the HR state and what leads to transition to FEP and to find a way of predicting the population prevalence of new cases to guide policy and service planning. There were several outputs of our programme:

- a web-deployed, evidence-based EIS planning tool for the NHS to predict the numbers of people requiring services by area
- knowledge of how best to detect HR for psychosis in primary care and schools
- a realistically complex understanding of person–place interactions in the genesis of HR and FEP.

The elements of our research programme are described below. We developed the Client Assessment Register (CAR), a user-friendly, computerised system that was used by clinicians and researchers within the team using local information technology systems and support. Our original intention was to use the information to develop an outcome assessment measure with considerable input from patients. Soon after we began the programme all NHS mental health trusts began to be encouraged to adopt the Health of the Nation Outcome Scales (HoNOS), later further developed for use as the ‘case mix’ adjustment for payment-by-results (PbR) funding of mental health services (HoNOS-PbR; treating people with more severe disorders and greater needs attracting greater funding from commissioners and vice versa). Understandably, our host NHS trust was keen to move wholesale to this measure, something that we supported even though it made some of our programme redundant.

Nevertheless, we significantly enhanced some aspects of the programme through an efficient use of available resources. For example, we systematically followed all individuals at HR for psychosis in the context of a separate study, the Prospective Analysis of At-risk mental states and Transitions into psycHosis (PAATH) study, with a naturalistic, observational design, not in our original application to the National Institute for Health Research (NIHR). This study was linked with several epidemiological and separately funded neurobiological research projects, representing an example of efficiencies in science and demonstrating the inter-relation between the different components of the programme.

© Queen’s Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Incidence of psychosis in socially and ethnically diverse settings

Much of our knowledge about the clinical epidemiology of psychotic disorders comes from studies based in predominantly urban settings, often cities, and predicated on outmoded health service models. These studies have indicated a rich landscape of variation in incidence according to standard epidemiological dimensions such as age, sex, social class and ethnicity, with further effects visible at the urban neighbourhood level including ethnic density. Far less is known about psychosis epidemiology and its public health impact across the gamut of population settlements, including mixed urban, suburban and rural populations.

Method

We estimated the administrative incidence of psychosis and its variation along sociodemographic dimensions using a case ascertainment system in a well-established EIS called CAMEO [see www.cameo.nhs.uk (accessed 18 January 2016)], with two linked teams serving a mixed urban–rural area. We built on our previous epidemiological studies, such as the East London First-Episode Psychosis (ELFEP) study and the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study. Also, by strategic alignment with other projects, such as the Social Epidemiology of Psychoses in East Anglia (SEPEA), we obtained useful data on the incidence of psychosis across eastern England.

Key findings

We estimated the overall incidence of FEP at 45.1 per 100,000 person-years [95% confidence interval (CI) 40.8 to 49.9 per 100,000 person-years]. Incidence rates varied across eastern England but were two to three times higher than those on which EIS specifications were predicated by the Department of Health. Our data suggest considerable psychosis morbidity in diverse, rural communities.

Development of a population-level prediction tool for the incidence of first-episode psychosis (PsyMaptic)

Using these rich epidemiological data we developed and validated a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder (PsyMaptic). Applied to FEP as proof of concept, we showed that it was possible to predict the expected incidence in a given population within the prediction intervals forecast by our models.

Key findings

A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in an EIS in East Anglia (95% CI 459 to 559 FEP participants), compared with 522 observed participants. The prediction tool for the incidence of psychotic disorders in England and Wales is freely available online [see www.psymaptic.org/ (accessed 18 January 2016)]. This is in use by NHS England to support new policies on EIS waiting time targets.

The Liaison with Education and General practiceS cluster randomised controlled trial: liaison with general practices to detect and refine referrals of people with at-risk mental states for psychosis

General practitioners are usually the first health professionals contacted by people with early signs of psychosis. It is unclear whether increasing the intensity of liaison between primary care and secondary care improves the clinical effectiveness and cost-effectiveness of detecting people with, or at HR of developing, a FEP. This is important given political commitments to facilitate early intervention and decrease waiting times in mental health. We developed and tested a theory-based intervention to improve detection and

referral of these mental states. In a parallel process we did the same in sixth-form colleges, as described in *Cluster randomised controlled trial with 16+ educational institutions to detect and refine referrals of people with at-risk mental states for psychosis*.

Developing the intervention in primary care

We used the theory of planned behaviour (TPB) to understand the factors that influence the identification of individuals at HR of developing psychosis in primary care. We then designed an intervention tailored to individual practices aiming to improve identification and referral of HR individuals and those with FEP.

Feasibility

We designed and assessed the psychometric properties of a questionnaire to determine and measure beliefs that influence GPs' identification of individuals at HR for psychosis in primary care. This work informed the subsequent design of the Liaison with Education and General practiceS (LEGS) educational intervention to help GPs detect these individuals.

Method

A semistructured discussion group elicited beliefs underlying GPs' motivations to detect these individuals and informed the construction of a preliminary 106-item questionnaire incorporating all constructs outlined in the TPB. A pilot phase involving 79 GPs from 38 practices across 12 counties outside the trial area defined the determinants of intention to identify HR individuals. Item response theory identified which items could be removed.

Key findings

The final instrument included 73 items and showed acceptable reliability ($\alpha = 0.77$–0.87) for all direct measures. Path analysis revealed that all of the TPB measures significantly predicted intention. Subjective norm, reflecting perceived professional influence, was the strongest predictor of intention. Collectively, the direct measures explained 35% of the variance of intention to identify individuals at HR, indicating a good fit with the TPB model. Information from the pilot questionnaire identified specific barriers and we designed strategies to change practice.

Cluster randomised controlled trial in primary care

Methods

The LEGS study was a cluster randomised controlled trial (cRCT) involving primary care practices (clusters) in the county of Cambridgeshire and Peterborough. Consenting practices were randomly allocated into two groups: (1) low-intensity liaison between primary care and secondary care, a postal campaign consisting of biannual guidelines to help in the identification and referral of individuals with early signs of psychosis and (2) the high-intensity intervention described in the previous section, which, in addition to the postal campaign, included a specialist mental health professional to liaise with each practice and support the theory-based educational package. Concealed randomisation involved a randomly permuted sequence in blocks, with 12 strata and 96 blocks. Practices that did not consent to be randomised constituted a practice-as-usual (PAU) group. The high- and low-intensity interventions were implemented over a period of 2 years for each practice during the study period April 2010 to October 2013.

The primary outcome was the number of HR referrals to the EIS per practice site predicated on an assumption that the intensive intervention would double them. New referrals were assessed clinically and stratified into those who met criteria for HR or FEP (together: psychosis true positives) and those who did not fulfil such criteria for psychosis (false positives). Referrals from PAU practices were also analysed.

An economic evaluation quantified the cost-effectiveness of the interventions and PAU, using decision-analytic modelling. Cost-effectiveness was expressed as the incremental cost per additional true positive identified.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Findings

Of the 104 eligible practices, 54 consented to be randomised. Twenty-eight practices were randomised to low-intensity liaison and 26 practices were randomised to the high-intensity liaison. Two high-intensity practices withdrew. High-intensity practices referred more HR [incidence rate ratio (IRR) 2.2, 95% CI 0.9 to 5.1; $p = 0.08$), FEP (IRR 1.9, 95% CI 1.05 to 3.4; $p = 0.04$) and true positive (IRR 2.0, 95% CI 1.1 to 3.6; $p = 0.02$) cases. High-intensity practices also referred more false positives (IRR 2.6, 95% CI 1.3 to 5.0; $p = 0.005$); most (68%) of these were referred on to appropriate services.

The total costs per true positive referral in high-intensity practices were lower than those in low-intensity or PAU practices; the high-intensity intervention was the most cost-effective strategy.

Interpretation

Increasing the resources aimed at managing the primary–secondary care interface provides clinical and economic value in this setting.

Cluster randomised controlled trial with 16+ educational institutions to detect and refine referrals of people with at-risk mental states for psychosis

As with GPs, teachers are in a good position to notice early signs of psychosis in their students but may not know enough about psychosis to recognise what they see or how to access appropriate help.

Development of the intervention

We designed an instrument to elicit teachers' commonly held beliefs about identifying students at HR according to the TPB. The study protocol employed in primary care was replicated in educational institutions for students aged 16+ years.

Key findings

The response rate to our teacher questionnaire was poor: only 75 (9.5%) returned questionnaires from the invited sample of 793 such that there will have been response bias. Perceived behavioural control was the strongest predictor of intention. Subjective norm did not predict intention. Collectively, the direct measures explained 37% of the variance of intention to identify HR for psychosis. Teachers believed that their peers or superiors might not approve of them identifying HR students. The greatest source of social pressure came from the senior management team within the school. Teachers' confidence and control over identification was low; they held a strong view that identifying HR symptoms in students was not part of a teacher's role. Our questionnaire proved to be reliable, with the analysis supporting the predictive power of the TPB with regard to intention. We have confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire to identify teachers' beliefs and intentions concerning the identification of individuals at HR for psychosis.

Status of the cluster randomised controlled trial

The pilot work informed the subsequent design of an educational intervention to help teachers detect HR students, replicating the methodology of the educational intervention in primary care. The implementation of the 2-year educational intervention and the subsequent 12-month counting of referrals is complete; statistical analysis continues.

The Prospective Analysis of At-risk mental states and Transitions into psycHosis

The principal objective of the PAATH study was to identify the proportion of individuals at HR for psychosis who make the transition into a psychotic illness and to elucidate the common characteristics that can help identify this population. Secondary objectives included various epidemiological and clinical analyses that would (1) contribute to an enhanced delineation of people at HR who are more likely to develop a full psychotic illness and (2) allow comparisons between HR and healthy volunteers (HVs) regarding sociodemographic and clinical characteristics, substance use, trauma history, functioning and quality of life.

Method

This prospective, naturalistic study assessed all individuals at HR for psychosis living in Cambridgeshire and Peterborough and detected during the duration of the trial, including those identified by GPs and 16+ educational institutions in the LEGS cRCT. Sixty help-seeking HR individuals, aged 16–35 years, were recruited from the CAMEO EIS in Cambridgeshire. Individuals were stratified into those who met the criteria for HR or FEP (true positives) according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) and those who did not (false positives). HR participants were followed up for 2 years, attending nine interviews (baseline and then every 3 months until the end of the study) at which they completed structured interviews and a battery of questionnaires on sociodemographic characteristics, diagnosis, psychiatric morbidity, trauma history, substance use and functioning. A random sample of 60 HVs matched for age (16–35 years), sex and geographical area underwent the same battery of questionnaires at baseline, 1 and 2 years.

Key findings

Transition rates from high risk to first-episode psychosis

Only 5% of our HR sample (3/60) made a full transition to a psychotic disorder based on structured clinical diagnosis (10% when CAARMS criteria were employed) over the 2-year follow-up period. This is an important message to young people with HR mental states and to services: the risk of transition from HR to FEP is low over 2 years.

Psychiatric morbidity, functioning and quality of life in people with high-risk mental states

High-risk individuals had a higher prevalence of moderate or severe depression, anxiety, obsessive–compulsive behaviours and suicidality than did HVs. HR individuals had poor global functioning and low quality of life that, combined with a significant risk of suicidality, justifies special attention from mental health services and appropriate care pathways. These findings, together with the low transition rates, suggest that clinical interventions in individuals at HR should aim at targeting a broader range of psychopathology, especially mood and anxiety symptoms, rather than just focusing on the treatment and/or prevention of psychosis.

Linked psychometric analyses in other population samples indicated that psychotic experiences measure the severe end of a common mental distress factor, consistent with these results.

Substance use

The prevalence of substance use was similar in HR individuals and HVs except for past polydrug use; this was higher for HR individuals. No HR individual or HV met the criteria for a current or lifetime *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition, text revision (DSM-IV TR) substance use disorder or dependence. The HR substance use profile of our sample was significantly different from that of HVs in the same geographical area, other HR samples and FEP patients in our region at the time of their referral to CAMEO. Their pattern of comparatively low use was unlikely to be a major trigger for transition to a frank psychotic disorder. The main difference between HR individuals and HVs was frequency of substance use. Current frequency of use was significantly higher in HR individuals than in HVs for alcohol and

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

cannabinoids. Higher frequency of substance use in HR individuals combined with a significantly younger age of first use could contribute to the development of psychotic-like experiences. Substance use represents a clinical domain that requires further emphasis and more detailed consideration.

History of psychological, physical or sexual trauma

High-risk participants experienced significantly more traumatic events than HVs, but equivalent distress. Occurrences of trauma and age at which trauma occurred were the most likely predictors of becoming HR, not the degree of distress reported as a result of the trauma. Bullying was not specifically assessed, which is a weakness of the study. To enable differentiation between dissociative responses to trauma and genuine prodromal psychotic presentations, trauma characteristics in HR individuals should routinely be thoroughly assessed; that said, these may be the same phenomena.

First-rank symptoms and premorbid adjustment

Almost half of the HR individuals in our sample had at least one Schneiderian first-rank symptom (FRS) traditionally thought of as particularly indicative of schizophrenia; 21.6% had more than one FRS. Auditory hallucinations and passivity experiences were the most frequent. Passivity experiences were the only FRS significantly associated with transition to FEP. During childhood HR individuals, especially those with FRSs, had poorer premorbid functioning and adjustment across educational, social and peer relationship domains than HVs. However, this did not predict transition 2 years later. FRSs might not predict merely psychosis but also various psychiatric disorders and/or long-term impairment because of abnormal developmental processes.

Ongoing analyses and future steps

This programme has resulted in a large collection of rich data. We are continuing to analyse clinical characteristics that may indicate possible transitions to FEP. Future publications will evaluate premorbid adjustment, personality and psychological variables related to self-perception and attachment. We outline in the report our collaborations with NIHR portfolio neurobiological projects investigating biological mechanisms underlying the HR state as an example of back translation.

Conclusion

This NIHR programme developed our understanding of the social epidemiology of psychosis and HR mental states. This has led to a population prediction tool for FEP in current use by commissioners in England. In terms of identification by GPs of FEP and HR mental states we have shown that the TPB can be used to change GP behaviour: the intervention doubled identification of HR individuals and FEP and was cost-effective; these results are also being used to influence national policy and practice. This programme resulted in primary and secondary mental health care working closely together.

We have added to the evidence that the HR or at-risk mental state has much in common with depression and anxiety; it is not necessarily a harbinger of psychotic disorder. We believe that this new understanding will help young people at HR receive appropriate services. We have made a demonstrable contribution to the international debate on clinical risk for psychotic disorders and the relationships between depression, anxiety and psychotic experiences in young people.

Trial registration

The primary LEGS trial is registered as ISRCTN70185866 and UKCRN ID 7036. The PAATH study is registered as UKCRN ID 7798.

Funding

Funding for this study was provided by the Programme Grants for Applied Research programme of the National Institute for Health Research.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

SYNOPSIS

Setting the scene

Psychotic illnesses such as schizophrenia and related conditions are a major concern for individuals, for society and for the NHS; they cause enormous disability and are expensive to treat. Developments in interventions have been slow. We have a clearer picture of the role of psychological therapies but the relative benefits of newer, expensive antipsychotic drugs remain uncertain.[1] However, services to deliver these interventions have changed over the last decade. For example, seminal work from around the world has led to the widespread adoption in the UK of crisis resolution and home treatment services for people with enduring mental illness such as schizophrenia, as set out in the *NHS Plan*.[2] In addition, a simple but radical idea concerning early-intervention services (EISs) and the evolution of psychosis through at-risk mental states has shaped service developments. Work by our research team and others has shown early developmental antecedents to psychosis.[3] As the illness becomes manifest, non-specific signs such as anxiety and depression develop and short-lived individual psychotic features form a prodrome to the full psychotic syndrome that may endure for months or even years before people seek help or receive treatment. This duration of untreated psychosis (DUP) is inversely related to outcome. Treatment in the prodrome (shortening DUP) may prevent the development of severe illness, improve outcome and lead to recovery in many cases.[4]

In addition to our disease focus on psychosis, this programme aimed to address a strategic issue for applied research and development (R&D) in the NHS. Although considerable amounts of clinical and social information data are processed daily within NHS and social care services, this information is disconnected from research so that it cannot be used to answer strategic questions. Many R&D developments are making important progress, but we wanted this programme to advance knowledge and understanding further by providing tools and a blueprint for connecting information, clinicians and patients in the search for the best services and interventions.

The problem we decided to tackle is cultural as well as structural.

Importance and relevance of the programme

Evidence for early intervention

At the time that our programme application was submitted the evidence base for EISs was emerging but was far from conclusive and, as ever, models successful in one area may not be suitable for another. Nevertheless, a clear blueprint was contained in the NHS *Mental Health Policy Implementation Guide*[5] and recent years have seen the rapid development of EISs across England for young adults aged 14–35 years; hence, individual-level randomised controlled trials (RCTs) of the effectiveness of early intervention are unlikely to be possible in England.

Epidemiology of high risk for psychosis

However, it was still not clear how early we should intervene as the natural history or epidemiology of individuals at high risk (HR) for psychosis was unspecified. As we began to appreciate the huge variability in the incidence of psychotic illness across different areas and communities in the UK,[6] it became clear that EIS planning was significantly hindered, with the likelihood of serious mistakes from over- and underprovision because the demand was not clear. EISs in some cities are overwhelmed whereas those in affluent suburban areas have capacity to spare.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The evidence–policy–practice gap

Identification of HR individuals was difficult and unfamiliar for staff in health and social care settings, let alone in education and other arenas where more applied research was required. We knew little about the causes of psychosis in individuals and could not fully explain the major variations in risk between regions. We aimed to close these gaps with this programme of applied epidemiological and observational research and a simple application of the cluster randomised controlled trial (cRCT) design (see *Work package 3*).

In addition to having been involved in independently funded trials of psychosocial interventions aimed at earlier intervention,[7] we had shown in our service that many people at an early stage of their psychotic illness have major cognitive problems that may underpin disability and be a realistic target for new interventions.[3] They also contribute to problems in functional outcome that are regarded by service users as more important than the symptoms and phenomena that professionals focus on. This functional recovery is what is important to people with psychosis, and we aimed to develop simple, patient-focused measures that could be used in everyday practice.

Unmet needs

There were gaps between the policy blueprint for EISs and existing evidence bases in epidemiology and prognosis. Furthermore, we highlighted the overarching gap between clinical practice and routine applied research.

We intended to exploit both the natural variance in our trust catchment area (Cambridgeshire and Peterborough), which covers an enormous range of demographic, social and environmental characteristics, and the planned and unplanned variation in service developments over time. With the help of recently developed statistical models for observational data we planned to build causal inferences from our observations.

We have an EIS called CAMEO [see www.cameo.nhs.uk (accessed 18 January 2016)] that includes two sister teams serving Cambridge and South Cambridgeshire, the deprived rural Fenland areas, prosperous market towns and the deprived inner-city areas of Peterborough. Our social and service variations give us sufficient capacity traction to ask, and answer, relevant questions.

By developing work from previous epidemiological and health services research studies, current descriptive research and work in our flagship EIS, CAMEO, we aimed to develop a programme of rolling observational studies and comparisons that could indicate what works and what does not work, and where a more formal RCT is needed (see *Work package 3* and *Work package 5*). We were fully aware of the strengths and weaknesses of observational designs and considered them as complementary methods to randomised designs to address relevant questions, funded through appropriate schemes. However, we included one cluster randomised element in this programme to tell us more about HR individuals and how to detect them (see *Work package 4*).

Innovation

One problem with HR mental states, despite their topicality, is that we knew little (nothing) about their epidemiology. Therefore, planning services was difficult. Population-based studies suggest that individual psychotic symptoms are common in young adults.[8] However, few people appear particularly disabled by a single symptom and, although they are linked with later development of psychotic illness, the vast majority of sufferers do not seek help; we do not know how these responses are related to illness. We needed to establish the epidemiology of early psychosis through case definitions such as, but not restricted to, HR, to foster appropriate help seeking and referrals.

Later in the illness it is clear that the incidence of diagnosable psychotic disorders varies hugely in terms of age, sex, ethnic mix and social geography of local communities. We had already shown marked heterogeneity in incidence according to age, sex, ethnicity and place in the three-centre Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study.[6] This has huge implications for EIS planners, for resource allocation decisions and for understanding where, when and why people become unwell. However, these findings are yet to be applied in a way that makes them immediately relevant to other places in the UK. Therefore, we investigated this in our diverse population and produced a service planning tool for the NHS to use nationwide (see *Work package 3*).

Original aims, objectives and outputs and eventual achievements

Our primary aim was to improve the identification, diagnosis and outcome of emerging and incident psychotic illness through a programme of research applied to service developments in our mental health trust. A secondary aim was to establish a system for applied R&D embedded in NHS services.

We consider that we achieved both of these aims in broad terms through a series of inter-related work packages (*Figure 1*), including the results of our cRCT on the identification and diagnosis of psychosis in primary care already informing NHS England commissioning guidance (see *Work package 4*); clinical studies on people with clinical HR mental states, function and quality of life (see *Work package 5*); a tool to predict the incidence of psychosis in geographical areas also informing front-line commissioning (see *Work package 3*); and evidence of successful embedding of researchers in clinical teams.

These successes are evidenced by our outputs for the objectives we set ourselves to achieve our aims. These are outlined below in advance of our fuller description of each work package, but here we also note where the objectives of our original programme were unsuccessful:

1. To define the incidence and social epidemiology of psychotic disorders and those at HR for psychosis in Cambridgeshire and Peterborough and establish cohorts for research that will allow us to understand causes and target services.
   Overall, this objective was achieved successfully in work package 3 (see *Work package 3*), with impact beyond Cambridgeshire and Peterborough to the national level. Research into the social and macrolevel environmental risk factors for first-episode psychosis (FEP) (see *Appendices 1* and *2*) led to the development of the PsyMaptic prediction tool [see www.psymaptic.org/ (accessed 18 January 2016) and *Appendix 3*], already in use by commissioners and incorporated into the NHS England commissioning guidance for EISs published in 2015.[9] In terms of causes of psychosis at this level, the work has defined and used the differences in incidence of psychosis in different localities such as population density and proportion of people in a community from black and minority ethnic groups, as well as other factors. Thus, the programme has informed national efforts to target EISs at a local level. This spatial epidemiology was extended to HR for the first time (see *Appendix 4*).
   The case ascertainment and assessment processes that we embedded within the NHS EIS, CAMEO, to underpin this epidemiological programme (see objective 2) also supported the Liaison with Education and General practiceS (LEGS) cRCT. The cohorts of patients with HR states have been used to support mechanistic and causal research projects funded through alternative sources, complementing our applied research; these are described in *Work package 5*.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

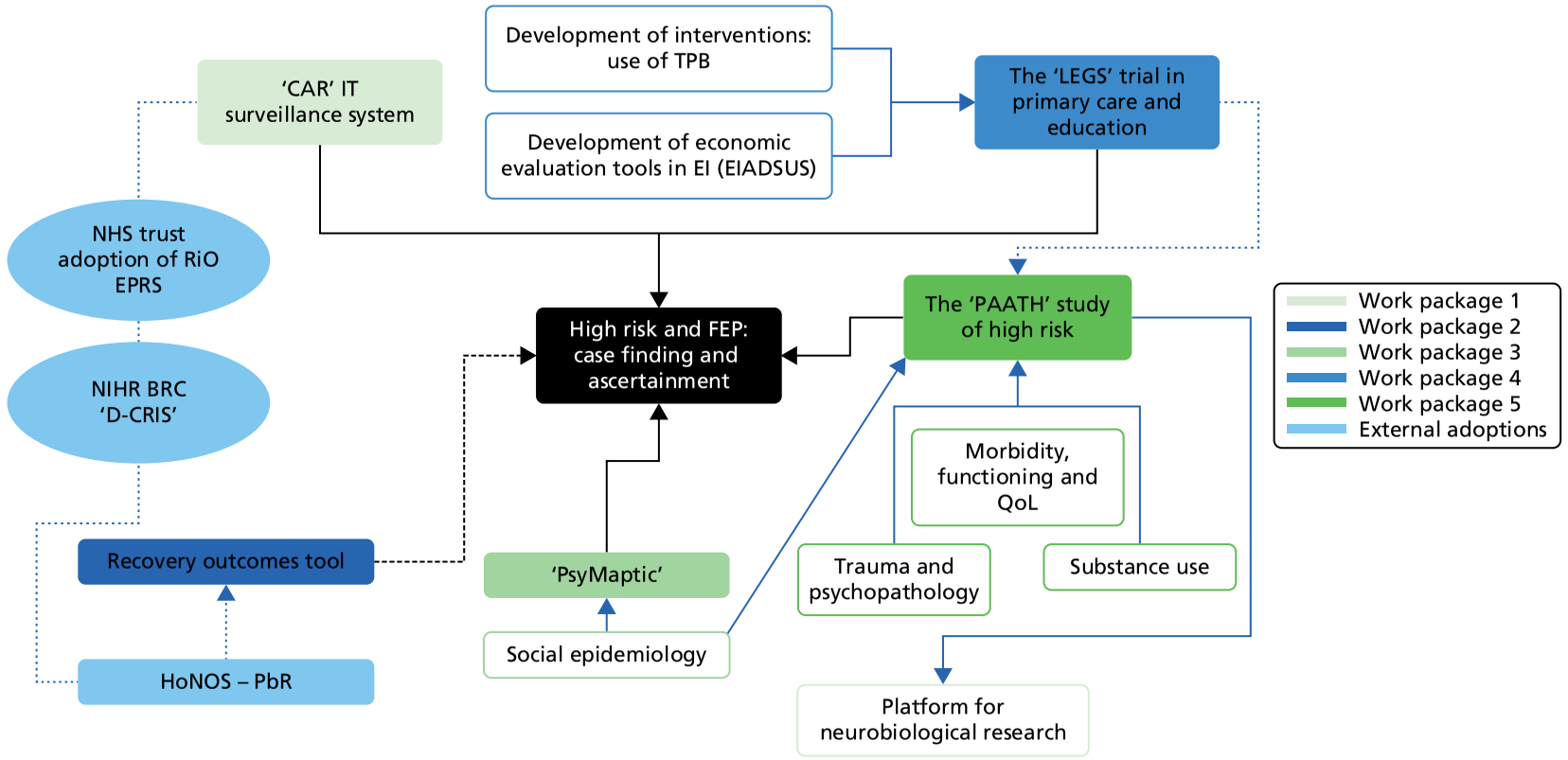


FIGURE 1 Diagram depicting the whole programme and its inter-relationships. BRC, Biomedical Research Centre; CAR, Client Assessment Register; CRIS, Clinical Record Interactive Search; D-CRIS, Clinical Record Interactive Search (Collaboration Programme); EI, early intervention; EIADSUS, Early Intervention Adult Services Use Schedule; FEP, first-episode psychosis; HoNOS-PbR, Health of the Nation Outcome Scales – payment by results; IT, information technology; LEGS, Liaison with Education and General practiceS; NIHR, National Institute for Health Research; PAATH, Prospective Analysis of At-risk mental states and Transitions into psycHosis; QoL, quality of life; RiO EPRS, RiO electronic patient record system; TPB, theory of planned behaviour. The neurobiological research associated with this programme was funded by the Medical Research Council and the Wellcome Trust.

2. To design reliable (efficient), brief and valid assessment procedures for case mix, service use and outcome for longitudinal studies of these clinical populations and to make these data available for prognostic research to study service variations.
   This objective was underpinned by work packages 1 and 2 (see *Work package 1* and *Work package 2*), in which there was mixed success. Some aspects did not go ahead whereas others developed in unforeseen but important ways.
   We describe in work package 1 the development of the Client Assessment Register (CAR), a user-friendly, computerised system that was used by clinicians and researchers within the team using local information technology (IT) systems and support. Our original ambition was to move this to a trust-wide mental health information system, not funded through the programme, to support routine clinical measurement at baseline and outcome, supporting the kind of observational studies in routine care that we had outlined in the application. In common with virtually all mental health trusts and most NHS trusts of any type, the implementation of a new IT system capable of supporting clinical work, management and research was problematic and protracted; it became clear early on that our plan would not be possible as our host trust decided to invest in the RiO electronic patient record system (EPRS) to meet its clinical and business needs.
   However, National Institute for Health Research (NIHR) funding in the mental health Biomedical Research Centre (BRC) at the South London and Maudsley (SLAM) NHS trust led to a prototypic system, the Clinical Record Interactive Search (CRIS) system, developed to provide researchers with regulated access to anonymised information extracted from electronic clinical records systems [see www.slam.nhs.uk/about/core-facilities/cris (accessed 19 January 2016)]. Originally designed for the SLAM electronic system, CRIS has now been extended as Clinical Record Interactive Search (Collaboration Programme) (D-CRIS) to five mental health trusts including the Cambridgeshire and Peterborough NHS Foundation Trust (CPFT), our host, and is running on our RiO electronic record system in shadow form. Thus, we were not able to implement this element of the programme, which itself was a major piece of IT development. However, this has been achieved at greater scale through larger investments in the SLAM NIHR BRC, and is being implemented in our trust at the time of writing.
   As we describe in work package 2, our original intention was to use the information to develop an outcome assessment measure with considerable input from patients. Soon after we began the programme all NHS mental health trusts began to be encouraged to adopt the Health of the Nation Outcome Scales (HoNOS),[10] later further developed for use as the 'case mix' adjustment for payment by results (PbR) funding of mental health services (HoNOS-PbR) (treating people with more severe disorders and greater needs attracting greater funding from commissioners and vice versa). Understandably, our host NHS trust was keen to move wholesale to this measure, something that we supported even though it made some of our programme redundant. Payment by results is not yet fully implemented as such.
3. To investigate the factors associated with transition from at-risk mental states to psychosis syndromes (true positives) and to characterise false-positive referrals.
4. To investigate the barriers to, and promoters of, functional recovery in at-risk mental states and early psychosis, in particular with relation to substance misuse.
   Work packages 4 and 5 underpinned the achievement of these two objectives, with the LEGS cRCT generating referrals of FEP or HR participants (true positives) or those with a range of other disorders (false positives). Standardised assessments and instruments such as the Comprehensive Assessment of At-Risk Mental States (CAARMS)[11] interview and the Mini-Neuropsychiatric Interview (MINI)[12] were used to classify individuals' mental health problems into psychiatric diagnoses.
   The finding of the LEGS cRCT (see *Work package 4*) that a high-intensity liaison approach between primary and secondary care doubled, as we hypothesised, referrals of FEP and HR mental states combined, of FEP alone and of HR individuals alone (the last of these not reaching statistical significance) is important; moreover, it saved money. Our combination of clinical effectiveness and cost-effectiveness methodology used in the trial was praised in a commentary that accompanied the publication of the LEGS trial[13] and the results were incorporated in the new NHS England commissioning guidance for early intervention in psychosis.[9]

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The cross-sectional follow-up of the cohort of people with HR mental states assembled through the true-positive referrals from the LEGS trial, collectively known as the Prospective Analysis of At-risk mental states and Transitions into psycHosis (PAATH) study (see *Work package 5*) was a success. The finding that people with mental states thought to put them at HR of psychosis almost invariably had one and often two non-psychotic diagnoses changes the way that we think about these presentations in that we should treat the disorders that they have (largely depression and anxiety), not the disorder that we think they may get (psychosis). Risk factors such as childhood maltreatment/trauma were investigated as was drug use.

5. To evaluate a range of effective interventions and service configurations that vary across our large mental health trust aimed at improving early identification outcome and promoting recovery.
   This objective was achieved in a narrow sense through the LEGS cRCT (see *Work package 4*), which compared two specific approaches to liaison between primary and secondary care in the identification and referral of new-onset psychosis and HR states and set these in the context of practice as usual (PAU). Our broader aim to have routine measures of baseline state and outcomes embedded in practice throughout our trust and supported by an effective IT system was not achieved, largely for the reasons outlined in our comment on objective 2. No mental health trust has this yet in routine practice although it, and the aspiration for ongoing, real-time observational assessment of alternative interventions delivered through different service configurations, remains on the horizon in mental health, particularly through developments such as CRIS, as it does in other areas of health care. Randomised designs on such a platform, most likely with adaptive methods to maximise both short-term patient benefit and long-term improvements in care, remain over the horizon but are being discussed at a conceptual level.[14]

The research elements that we employed to achieve our objectives are described in the work packages of this report. The publication outputs are mostly included as appendices (*Table 1*).

TABLE 1 Alignment of programme objectives, work packages and outputs as presented in the report

Programme objectives	Synopsis: research development	Description of programme outputs
To define the incidence and social epidemiology of psychosis	Work package 3: incidence and social epidemiology of psychosis (see *Work package 3*)	*Appendices 1–4*
To design reliable, brief and valid assessment procedures	Work package 1: IT systems (see *Work package 1*)	CAR IT surveillance system and CRIS (external adoption)
	Work package 2: development of a tool to measure recovery (see *Work package 2*)	HoNOS-PbR (external adoption)
To investigate the factors associated with transition from HR	Work package 5: follow-up of referrals of individuals identified as being at HR for psychosis (see *Work package 5*)	*Appendices 9–12*
To investigate the barriers to, and promoters of, functional recovery in HR	Work package 5: follow-up of referrals of individuals identified as being at HR for psychosis (see *Work package 5*)	*Appendices 9–12*
To evaluate a range of effective interventions and service configurations	Work package 4: detecting and refining referrals of individuals at HR for psychosis (see *Work package 4*)	*Appendices 5–8*

Patient and public involvement throughout the programme

As outlined in our programme grant application, we have a strong commitment to public involvement in research in the context of a mental health partnership trust and therefore patient and public involvement (PPI) has been paramount.

Involvement has been prominent in all phases. It forms a blueprint for our service development within CAMEO. We stress our commitment to research as a means of improving practice in the initial information materials that service users and their carers receive. All are invited to take part in research with the emphasis on this being entirely their own decision. We have a high (> 50%) prevalence of people becoming involved so we can tailor our research to answer questions that are relevant to them. We run dissemination 'research groups' for our service users and carers, keeping them informed and promoting discussion of new ideas, methods and projects. We always have a carer (family) and/or a user on interview panels for research staff when there is patient contact.

In the current programme a service user's mother sparked the idea of working with general practitioners (GPs) and schools to try to improve detection and referral. PPI was vital for the development of the information sheets and assessment tools that we designed; if the tools were not useful to patients, they were not useful at all.

The pilot study that informed our LEGS trial (see *Work package 4*) interventions included 84 GPs and a similar number of teachers outside the trial area. Their contributions and comments were a significant asset in the development of interventions based on the theory of planned behaviour (TPB)[15] and within the Medical Research Council framework for the development and evaluation of complex interventions.[16]

As part of the high-intensity intervention for general practices and colleges, educational digital versatile discs (DVDs) were produced (see *Work package 4*). They required input and advice from service users and college students. Two GPs, two teachers, two service users, two college students and one professor of psychiatry participated in developing the content of the scripts and production. These DVDs have been highly regarded by GPs and teaching staff participating in the LEGS trial.

All primary care practitioners and teachers involved in the LEGS trial have had the opportunity to contribute with comments and impressions through a biannual newsletter. These comments were taken into account to facilitate the practical implementation of the trial, except when they could potentially affect aspects related to methodological aspects of the study protocol.

With regard to the follow-up of HR referrals (the PAATH study; see *Work package 5*), we developed a comprehensive database to collect relevant epidemiological, clinical, functional and quality of life information. One of the peer support workers working in the CAMEO clinical team, where this research is embedded, participated in the design of the database and has facilitated its use enormously. His clinical knowledge and experience as a service user contributed to making it meaningful and easy to analyse. He has closely worked with our IT project manager and psychometrician.

Our research team, particularly JP, has built up innovative partnerships with mental health charities such as Squeaky Gate, an extraordinary and creative charity that empowers people with mental health problems through music and the arts [see www.squeakygate.org.uk (accessed 19 January 2016)], especially during the so-called Squeaky Gate Galas featuring 'Inside an Unquiet Mind' that usually take place in Cambridge during the annual Science Festival. This has been an excellent collaboration to publicise research such as the LEGS cRCT (see *Work package 4*) and the PAATH study (see *Work package 5*). These performances are open to the general public. For example, last year more than 500 people watched these plays. They were very well received by the public and also had a significant repercussion in the scientific literature. Indeed, the *EMBO Journal*, from Nature publishing group, invited us to write an article on this new venture.[17]

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The significant evolution of PPI in research during the last few years has been challeging at times as we had to adjust our initial objectives and plans to new and more desirable requirements. However, we feel that this progression has eventually become seamless. Now, we would naturally have included a service user or carer with research experience as a co-applicant, but at the time that the application for this programme was submitted current guidance did not recommend this; things have moved on. However, we included GPs and sought teachers' advice in our steering groups and, as set out above, have included PPI: a patient and carer have helped with the construction of this report, including having some detailed input to the *Abstract, Plain English summary* and *Scientific Summary*.

We are committed to disseminating our results using all possible channels to reach patients and the public. We have excellent links with charities (see above) and third-sector organisations such as Rethink [see www.rethink.org/ (accessed 20 January 2016)]. We also have excellent relationships with commissioners who will advise about the best way to communicate findings that emerged from this programme. We will also provide information about the results to participants with their approval and will organise meetings to feed back our findings. We have a programme arranged to execute our strategy to further disseminate results to the public.

The following statement is not strictly related to PPI but is a fair reflection of what the research team, along with PPI, accomplished in making materials successful and worthwhile in the LEGS cRCT. This feedback was sent to us by a nurse working in a large college of further education:

> *Cambridge Regional College (CRC) has a population of approximately 5000 full-time students. About 1/10 students are referred to/seek help at Student Services for emotional and mental health issues. The majority of our students are aged 16-25, and a large quantity come from challenging backgrounds (e.g. abuse, domestic violence, homelessness, and substance abuse etc). Consequently, there are high risks for students developing poor emotional health and (sometimes chronic) mental health issues. Early identification and referral is critical to the students' well-being and ability to achieve their college goals. Participating in the LEGS trial has provided staff at CRC an opportunity to increase their knowledge and understanding of psychosis (clarification of the condition, and how and when it can present). Staff were extremely positive about the CAMEO training on September 8th 2011 (to which about 50 people attended); staff stated that it increased their confidence in detecting early symptoms (indicative of psychosis), and making referrals to appropriate professionals. The laminated posters/flyers (which were displayed in staff rooms and offices), are reported to be useful resources in reminding staff what to look out for. Prior to the LEGS trial, many tutors, teachers and staff found the term 'psychosis' intimidating, and were not confident in dealing with the issue. Since the LEGS trial this year, many staff have stated their overall response to psychosis has improved. As the mental health practitioner at the college, I have noticed an increase in the number of students being referred to Student Services with symptoms possibly pertaining to psychosis (e.g. delusions and hallucinations) this academic year. Staff have also been quicker to identify students with unusual presentation (e.g. uncharacteristic affect/behaviour, lack of concentration/attendance) and refer them to review and identify any core underlying issues. Over the last year, there has been a significant shift and improvement in attitudes and approaches to mental health at CRC, and the LEGS trial has played a part in this. As a result of this shift, more students have been able to have their needs assessed and (if necessary) receive the appropriate support and treatment. With the right interventions, more students have been able to complete their academic courses/qualifications this year. As a professional, it is my priority to support the early identification of mental health issues, so students have the best possible treatment and prognosis. I have made several referrals to CAMEO this year, and have been extremely pleased with the quick response and quality of CAMEO's assessment and advice. The feedback from students referred to CAMEO has generally been very positive too. Students have expressed they feel 'comfortable' talking to the CAMEO team, and have appreciated having their issues 'taken seriously' and advised accordingly. For many students being referred to a specialist mental health agency is a scary experience (for many reasons e.g. 'I must be crazy now', and 'doctors and diagnoses' are often involved). However, CAMEO's approach has reassured students, and many have been onto the CAMEO website for further information. Overall, Cambridge Regional College has benefited from participating in the LEGS trial, and looks forward to further information and involvement with CAMEO.*

Work package 1: information technology systems

Development and implementation of the Client Assessment Register

In support of various data collection requirements for service outcomes, evaluation and research trials, we have developed and implemented a clinical surveillance system to identify and electronically record all cases of clinically relevant psychotic states. This information has been gathered through predetermined sets of assessment batteries that can be modified according to clinical or research requirements. The system integrates with the central care records system of the trust to avoid data redundancy. This process synchronises with the centralised system's basic sociodemographic data on a daily basis. The data are only editable in the central system and several data validity checks are built into the system to ensure improved data quality.

The CAR system consists of a front-end application interface designed according to industry-acceptable development standards. The front end was developed in a Visual Basic Integrated Development Environment and works on a client–server topology (*Figure 2*). The database side of the system was developed in Microsoft Transact Structured Query Language (Transact-SQL) database format (Microsoft Corporation, Redmond, WA, USA) and uses an Open Database Connectivity (ODBC) client to connect and transmit data.

As a reporting function the CAR system also allows for data to be exported from the database into external data sources such as Microsoft Excel, for analysis and manipulation for statistical analysis.

To ensure that the system stays in line with future technological development we also created a mobile module for remote capturing and reporting of the CAR data. The enhancement allows service users and staff to remotely capture a specific battery of assessments on an iPad or any tablet device that can connect to the internet and have browsing capabilities. This is achieved through a web-based application that is enhanced using the Visual Basic.NET framework. The system also allows service users to enter data. Through the scoring system, staff can immediately access the outcome of particular self-assessments, which may have clinical implications. They can then act accordingly by putting the necessary procedures in place.

During the LEGS cRCT the system was supported and maintained by an appointed IT development and project manager. This staff member was also responsible for training members of staff and service users to ensure the best quality of data capture.

The team also had access to a trust-wide data library that stores the clinical documents of trust service users. The Clinical Documents Library is a bespoke web-based solution that provides a user-friendly, secure single point of access for all authorised users throughout the trust. The library stores clinical letters, reports and assessments against service user records.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

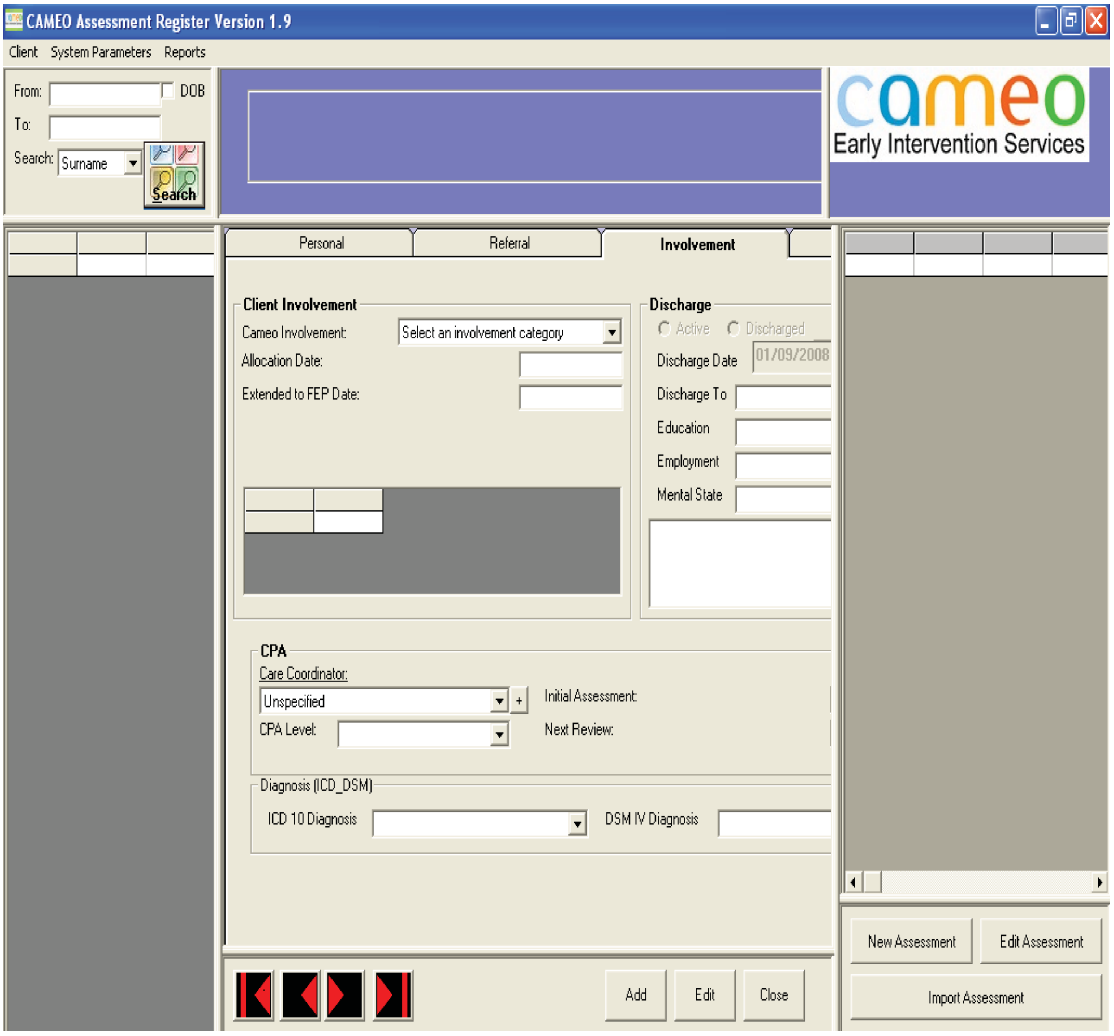


FIGURE 2 Screenshot of the CAR constructed for the programme and available from the authors.

An initial requirements report recognised that existing ways of sharing clinical documents at various locations presented inefficiencies and the recommended approach is consistent with the trust's strategic vision and principles within the Way Ahead Programme [see www.wayaheadcare.co.uk/quality-assurance.php (accessed 20 January 2016)]. The following details some of the features of the new system:

1. enables service user records to be held at a central location
2. enables a single standardised way of storing and sharing clinical documents
3. provides a secure library of clinical documentation
4. is available to all authorised clinicians throughout the trust
5. reduces time spent by staff looking for documents
6. reduces data redundancy
7. provide electronic versions of clinical information.

As stated earlier, our final goal was to implement our CAR information system at a trust-wide level, not funded through the programme, to support routine clinical measurement at baseline and outcome. In common with virtually all mental health trusts and most NHS trusts of any type, the implementation of a new IT system capable of supporting clinical work, management and research was problematic and protracted; it became clear early on that our plan would not be possible as our host trust decided to invest in the RiO EPRS to meet its clinical and business needs.

However, the NIHR BRC for mental health at the SLAM NHS Foundation Trust developed a prototypic system, the CRIS system, to provide regulated access to anonymised data from electronic patient records systems (see www.slam.nhs.uk/about/core-facilities/cris). Although the CRIS system was initially designed for SLAM NHS Foundation Trust systems, it has now been implemented as D-CRIS in several mental health trusts, including CPFT, our host, where it is running on and shadowing the RiO EPRS. Thus, we were not able to extrapolate this element of our programme, which itself was a significant IT development that was already completed and significantly contributed to the success of this programme, especially the LEGS cRCT and the PAATH study. Nevertheless, this ambitious objective has been achieved through larger investments in CRIS/D-CRIS by the NIHR BRC for mental health.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Work package 2: development of a tool to measure recovery

With regard to work package 2, we proposed to develop psychometrically and practically acceptable instruments and test them in practice to understand predictors of and barriers to recovery. Through measurement innovation we intended to create tools and the culture that could sustain (indeed welcome) constant evaluation of service structure and interventions. We considered this fundamental to guide service planning. However, this was partly resolved with the gradual adoption during the programme of the HoNOS[10] by our NHS trust. As stated in our application, this simple tool was already employed in Scandinavia and Australia, but not in the UK. Its eventual adoption by the NHS significantly reduced the importance and viability of this element in our research plan. Furthermore, HoNOS seem to possess satisfactory sensitivity and validity to be used in routine assessment within early-intervention programmes.[10] The HoNOS have become the basis of PbR for mental health (as HoNOS-PBR) nationally, and our trust was in line with others by adopting them. We were disappointed not to be able to produce a psychometrically sophisticated tool for use in clincal practice but delighted that the services are using a recognised tool.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Work package 3: incidence and social epidemiology of psychosis

In this work package we describe the administrative incidence (these are data not primarily collected for research purposes) and social epidemiology of psychotic disorders and HR for psychosis in Cambridgeshire and Peterborough. This was mainly intended to help understand the complex person–place interactions in the genesis of schizophrenia and other psychoses as a useful, less immediately applied but ultimately essential goal in terms of the future prevention of disability from such disorders.

To continue with our endeavour of understanding who we treat, where they come from, what is wrong, what we do for them and what happens to them, we built on our clinical and research experience in the local Cambridge EIS (CAMEO) as it expanded in stages to cover all of Cambridgeshire and Peterborough, a socially and ethnically diverse area of 800,000 people. By our alignment with other regional research projects, such as the Social Epidemiology of Psychosis in East Anglia study [SEPEA; see www.sepea.org (accessed 19 January 2016)], we also evaluated comparative epidemiological data for the whole of East Anglia.

These findings were compared with wider data that we have collected with other academic partners, such as the ÆSOP[6] and East London First-Episode Psychosis (ELFEP)[18] studies, to devise realistically complex statistical models of psychosis incidence.

As a result of this, we developed a web-deployed clinical epidemiology tool that will predict the numbers of people who will develop new psychotic illnesses by social geography, demographics and area, to facilitate future NHS planning. Any health economy will be able accurately to predict morbidity in its area, taking into account detailed characteristics of its population (available from census data). This will promote the right services in the right places.

In this context we also developed and implemented clinical surveillance and IT systems to identify and electronically record all cases of clinically relevant psychotic syndromes in Cambridgeshire and Peterborough, linking with routine data capture for the Mental Health Minimum Data Set (MHMDS) requirements.[19] This represented a culture change within a predominantly clinical service that we implemented successfully.

Incidence of psychosis in socially and ethnically diverse settings

See *Appendix 1* for the published report of this work.[20]

Research aims

The aim of this study was to compare the observed with the expected incidence of psychosis and delineate the clinical epidemiology of FEP using epidemiologically complete data from the CAMEO EIS over a 6-year period in Cambridgeshire for a mixed rural urban population.

Methods for data collection

Data came from a population-based study of FEP [*International Classification of Diseases*, 10th revision (ICD-10), F10–39[21]] in people aged 17–35 years referred between 2002 and 2007; the denominator was estimated from mid-year census statistics. Sociodemographic variation was explored by Poisson regression. Crude and directly standardised rates (for age, sex and ethnicity) were compared with pre-EIS rates from two major epidemiological FEP studies conducted in urban English settings.[6,18]

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Analysis

Incidence per 100,000 person-years was calculated with 95% confidence intervals (CIs). Incidence rate ratios (IRRs) were calculated (with 95% CIs) using Poisson regression to control for possible confounding. We conducted a sensitivity analysis on subjects with missing ethnicity data by repeating the Poisson regression four times, assuming that all such subjects belonged to the white British, non-British white, black and other ethnic groups in turn. The likelihood ratio test was applied to assess statistical interactions and model fit.

Key findings

There were 285 cases over 569,921 person-years (aged 16–35 years), yielding a crude incidence of 50.0 per 100,000 person-years (95% CI 44.5 to 56.2 per 100,000 person-years), higher than anticipated and comparable with estimates from more urban UK settings. These comparisons were with rates on which EISs were predicated and also with incidence rates from the two recent observational studies of FEP covering four urban catchment areas of the UK: east London and south-east London, Nottingham and Bristol.[6,18] These comparisons are shown in *Figure 3*.

Rates in men were double those in women and declined with age for both sexes. After adjustment for age and sex, rates were elevated for people from black ethnic groups (IRR 2.1, 95% CI 1.1 to 3.8). The increased risk of psychosis among people of black ethnicities demonstrated in this study was smaller than that seen in other studies.

The administrative incidence of psychosis calculated from within an EIS in a mixed urban–rural setting was similar to estimates from city-based studies and higher than originally predicted when EISs were designed in the UK. The sociodemographic characteristics of incidence rates were also similar to those of more urban studies, including higher rates in black and ethnic minority groups, indicating that psychosocial and other phenomena contributing to this variation are not confined to urban populations. Adjustment of city rates for ethnic structure of the population reduced high city rates markedly, indicating the importance of this factor to the high burden of FEP in cities. This has implications not only for our understanding of the determinants of psychosis but also for service planning.

The crude incidence rates presented from the CAMEO EIS were more than three times higher than anticipated by the original service planning estimates from the Department of Health in 2001. Possible explanations for this are:

1. There has been little evidence on incidence in rural settings compared with urban areas, such that the assumptions about overall rates in the general population have simply been wrong.
2. EISs are particularly effective in eliciting referrals of true positives and engaging them long enough for assessments to be made. That said, the fact that we did not have a formal leakage study, as was undertaken in our comparison samples, suggests to us that those studies and general mental health services did not massively underestimate morbidity.
3. More rural areas may look like cities because of the uniformly high prevalence of cannabis use by young people in the UK.
4. The most obvious reason for the discrepancy between our data and the figure for EIS planning used in England (around 15 per 100,000 person-years) is that the latter is predicated largely on the incidence of schizophrenia whereas we know that only around one-third of FEP is classified as such at first presentation.
5. The incidence of psychosis is higher in young adults aged 14–35 years than in the population as a whole, and EISs are targeted at the former group.

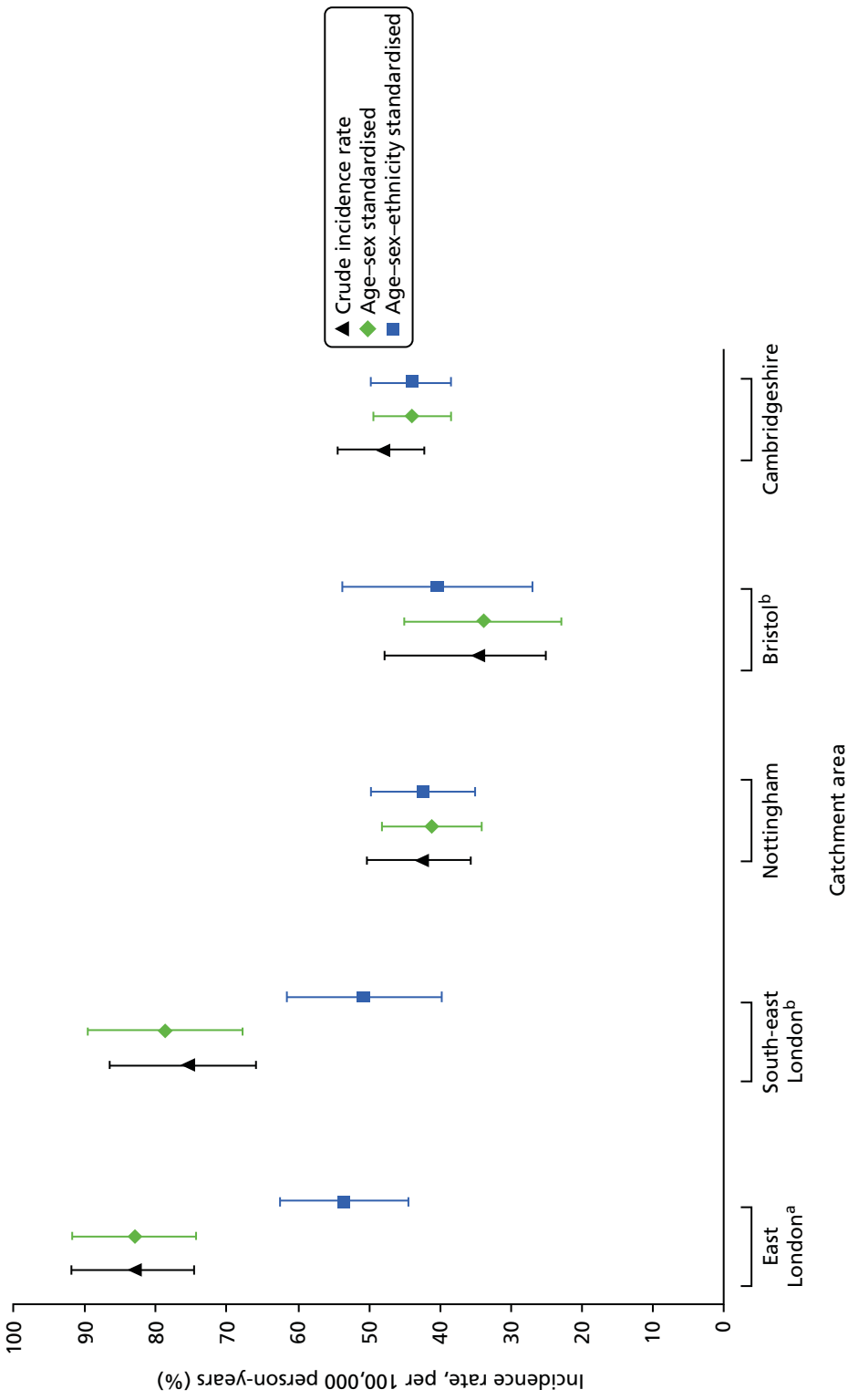


FIGURE 3 Comparison of crude and directly standardised incidence rates in Cambridgeshire and the four catchment areas of the ÆSOP[6] and ELFEP[18] studies. Directly standardised to the population of England aged 18–34 years estimated in the 2001 census. a, Data made available from the authors;[18] b, data made available from the authors.[6]

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Limitations

Because of the lack of routine incidence data at the time of the study, we were unable to compare incidence rates presented here with those in our study population prior to the start of the CAMEO service. This is necessary to determine precisely whether or not EISs do identify excess morbidity.

Incidence of psychosis across Eastern England

See *Appendix 2* for the published report of this work.[22]

Research aims

The aim of this research was to present the initial 18-month findings from the SEPEA study, a large, 3-year population-based FEP study of incepted incidence observed through five EISs.

Methods for data collection

We established a surveillance system to record sociodemographic and clinical data on all people aged 16–35 years resident within East Anglia who were referred to and accepted by our EIS with FEP over the 3 years from 1 August 2009. ICD-10[21] clinical and research (OPCRIT[23]) diagnoses for psychotic disorder (F10–39) are established at 6 months and 3 years after referral.

Analysis

Poisson regression explored covariate effects. The full method is given in the online supplement [see http://bjp.rcpsych.org/content/suppl/2011/12/19/bjp.bp.111.094896.DC1.html (accessed 21 September 2014)].

Key findings

We identified 357 eligible subjects (incidence 45.1 per 100,000 person-years, 95% CI 40.8 to 49.9 per 100,000 person-years). Rates varied across the EISs but were two to three times higher than those on which services were commissioned.

Risk decreased with age, was nearly doubled among men and differed by ethnic group: it was doubled in people of mixed ethnicity but was lower for those of Asian origin than for the white British population (*Table 2*).

Psychosis risk among ethnic minorities was lower than reported in urban settings, which has potential implications for aetiology if whatever factors increase risk in people from black and minority ethnic groups in cities are less potent, rare or absent in rural areas. Overall, our data suggest considerable psychosis morbidity in diverse, rural communities.

TABLE 2 Sample characteristics and adjusted rate ratios in the SEPEA study at 18 months

Variable	Participants, *n* (%)	Denominator, *n* (%)[a]	Adjusted[b] relative risk (95% CI)
Total	357 (100)	838,574 (100)	–
EIS (*n* = 357)			
Cambridgeshire, Peterborough and Royston	122 (34.2)	306,283 (36.5)	–
West Norfolk	17 (4.8)	41,765 (5.0)	–
Central Norfolk	91 (25.5)	219,860 (26.2)	–
Great Yarmouth and Waveney	38 (10.6)	69,218 (8.3)	–
Suffolk	89 (24.9)	201,448 (24.0)	–
Sex (*n* = 330)			
Women	115 (34.8)	405,221 (48.3)	1
Men	215 (65.2)	433,353 (51.7)	1.7 (1.4 to 2.2)
Age group (years) (*n* = 330)			
16–17	52 (15.8)	71,929 (8.6)	1
18–19	53 (16.1)	88,976 (10.6)	0.8 (0.6 to 1.2)
20–24	118 (35.8)	219,157 (26.1)	0.7 (0.5 to 1.0)
25–29	73 (22.1)	213,385 (25.4)	0.5 (0.3 to 0.7)
30–35	34 (10.3)	245,127 (29.2)	0.2 (0.1 to 0.3)
Ethnicity (*n* = 330)			
White British	261 (79.1)	671,588 (80.1)	1
White non-British	21 (6.4)	50,882 (6.1)	1.2 (0.8 to 1.9)
Mixed ethnicity	15 (4.5)	17,364 (2.1)	2.1 (1.3 to 3.6)
Black	12 (3.6)	18,471 (2.2)	1.8 (1.0 to 3.3)
Asian	12 (3.6)	69,014 (8.2)	0.5 (0.3 to 0.9)
Other ethnicities	9 (2.7)	11,255 (1.3)	2.3 (1.2 to 4.5)

a Adjusted for duration of case ascertainment in each EIS (18 months).
b Adjusted for other variables in the model (age group, sex and ethnicity).

Note
Because the study is ongoing, detailed sociodemographic data were available only for a subset (*n* = 309) of the total incidence sample (*n* = 378). Thus, incidence rates were reported when we had data on the full sample (*n* = 378), with relative risks reported from Poisson regression on demographic data for the subsample (*n* = 309).

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Development of a population-level prediction tool for the incidence of first-episode psychosis (PsyMaptic)

See *Appendix 3* for the published report of this work.[24]

Research aims

Although the true incidence of FEP varies enormously according to sociodemographic factors, a single estimate of population need was used universally for developing EISs in the UK. Therefore, we sought to develop a realistically complex, population-based prediction tool for FEP, based on precise estimates of epidemiological risk.

Methods for data collection

Data from 1037 participants in two cross-sectional population-based FEP studies[6,18] were fitted to several negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at risk of a third, socioeconomically different region to predict the expected caseload over 2.5 years, where the observed rates of ICD-10 F10–39 FEP had been concurrently ascertained through EISs.

Analysis

The main outcome measure was observed counts compared with predicted counts [with 95% prediction intervals (PIs)] at EIS and local authority district (LAD) levels in East Anglia to establish the predictive validity of each model. For the full analysis see *Appendix 3*.

Key findings

The use of modelling with epidemiological data from two large studies of FEP in England[6,18] produced accurate FEP forecasts.

Negative binomial regression models with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EISs in East Anglia (95% PI 459 to 559 FEP participants) compared with 522 observed participants. This model predicted correctly in five out of six EISs and 19 out of 21 LADs.

Our data suggested that the original figure used to commission EISs probably overestimated the true incidence of FEP in rural areas and underestimated rates in urban settings.

The initial assessment of some people who do not require subsequent EIS care means that additional service resources will be required.

Successes

All models performed better than the current gold standard for EIS commissioning in England (716 cases, 95% PI 664 to 769 cases). We have developed a prediction tool for the incidence of psychotic disorders in England and Wales, made freely available online (see www.psymaptic.org/), to provide health-care commissioners with accurate forecasts of FEP based on robust epidemiology and anticipated local population need (*Figure 4*). This has already been used for service planning in London and, at the time of writing, is being used by NHS England to support the national early intervention waiting time standard and target. The work also appeared in the *Annual Report of the Chief Medical Officer 2013* [see www.gov.uk/government/uploads/system/uploads/attachment_data/file/413196/CMO_web_doc.pdf (accessed 19 January 2016)].

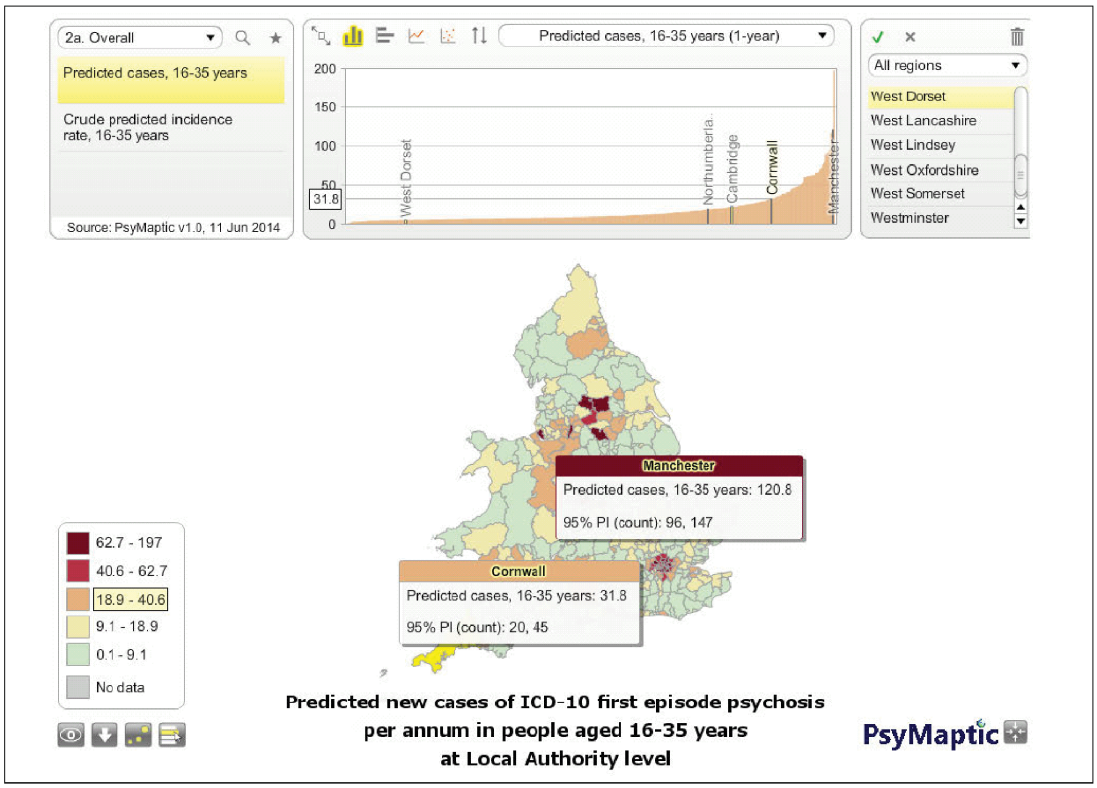


FIGURE 4 Example of PsyMaptic interactive image. Source: www.psymaptic.org/.

Limitations

Although our models provide estimates of the expected clinical burden of FEP in the community, services may see a broader range of psychopathology, consuming resources, or incepted rates may be influenced by supply-side organisational factors.

It was not possible to validate our prediction tool in settings outside of England and Wales or for specific psychotic disorders. As data become available we will assess the use of our prediction tool in other settings and for disorders.

Social and spatial heterogeneity in psychosis proneness

See *Appendix 4* for the published report of this work.[25]

Research aims

To test whether spatial and social neighbourhood patterning of people at HR of psychosis differs from that of FEP participants or control subjects (healthy volunteers; HVs) and to determine whether or not exposure to different social environments is evident before disorder onset.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Methods for data collection

First-episode psychosis participants were identified through the SEPEA study. HR participants were identified as part of the PAATH study, which ran in parallel to the SEPEA study in CAMEO. Control participants were identified from an embedded project within the SEPEA study, the European Union Gene–Environment Interaction (EU-GEI) study [see www.eu-gei.eu/ (accessed 19 January 2016)], an international, multicentre case–sibling–control study of gene–environment interactions in schizophrenia and other psychoses in people aged 18–64 years. Using a NIHR Primary Care Research Network (PCRN) initiative designed to assist with recruitment of participants from primary care for research, HVs who met the inclusion criteria (aged 18–64 years; no previous history of psychosis) were randomly selected from 10 GP practice patient lists within the Cambridgeshire and Peterborough catchment area.

Analysis

We tested differences in the spatial distributions of representative samples of individuals with FEP, HR participants and HVs and fitted two-level multinomial logistic regression models, adjusted for individual-level covariates, to examine group differences in neighbourhood-level characteristics. For full techniques see *Appendix 4*.

Key findings

The spatial distribution of HVs ($n = 41$) differed from that of HR participants ($n = 48$; $p = 0.04$) and FEP participants ($n = 159$; $p = 0.01$), whose distribution was similar ($p = 0.17$). Risk in FEP and HR groups was associated with the same neighbourhood-level exposures: proportion of single-parent households [FEP adjusted odds ratio (aOR) 1.56, 95% CI 1.00 to 2.45; HR aOR 1.59, 95% CI 0.99 to 2.57), ethnic diversity (FEP aOR 1.27, 95% CI 1.02 to 1.58; HR aOR 1.28, 95% CI 1.00 to 1.63) and multiple deprivation (FEP aOR 0.88, 95% CI 0.78 to 1.00; HR aOR 0.86, 95% CI 0.76 to 0.99).

The pattern of elevated risk at the neighbourhood level was similar for both HR and FEP participants relative to HVs (*Figure 5*).

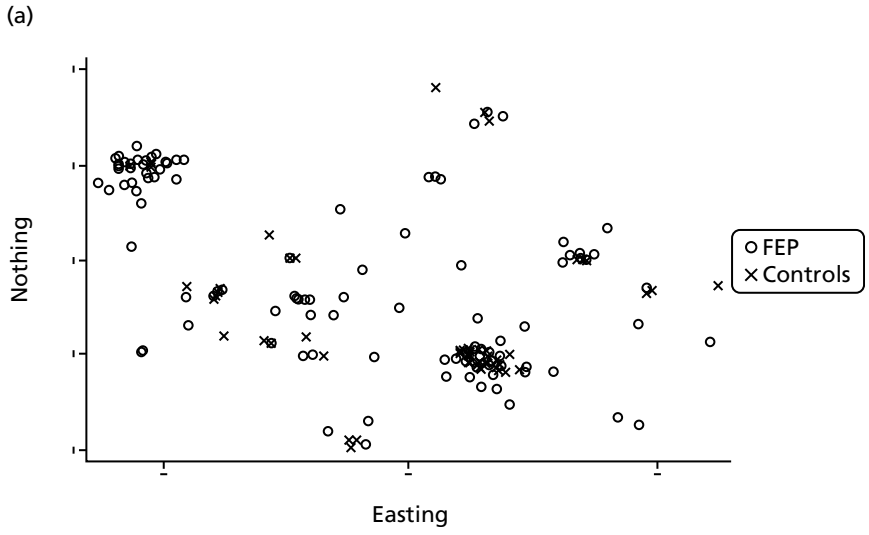


FIGURE 5 Spatial locations of participants by status. The spatial distribution of control subjects (HVs) was significantly different from that of both (a) people with FEP ($p = 0.01$) and (b) the HR group ($p = 0.04$) under a two-dimensional *M*-test. There was no statistically significant difference in the spatial distribution of (c) FEP and HR participants ($p = 0.17$). The spatial distribution of (d) people with non-affective FEP and people with affective FEP was also significantly different from each other ($p = 0.01$). Locations are based on postcode centroid at first contact. Axis scales are plotted according to British National Grid co-ordinates of residential postcode at first contact, but the co-ordinates and scale have been removed to preserve sample anonymity. (*continued*)

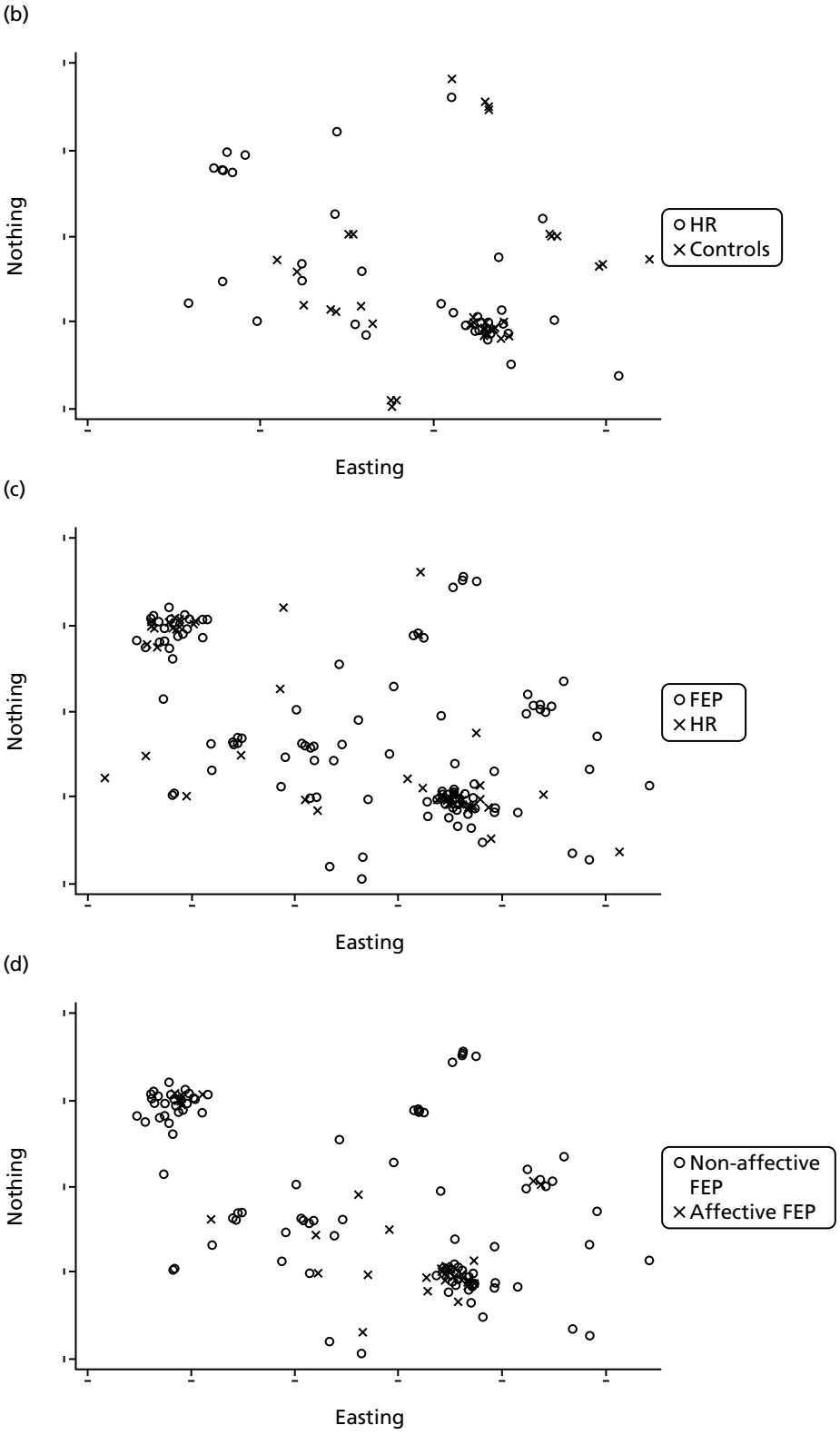


FIGURE 5 Spatial locations of participants by status. The spatial distribution of control subjects (HVs) was significantly different from that of both (a) people with FEP ($p = 0.01$) and (b) the HR group ($p = 0.04$) under a two-dimensional *M*-test. There was no statistically significant difference in the spatial distribution of (c) FEP and HR participants ($p = 0.17$). The spatial distribution of (d) people with non-affective FEP and people with affective FEP was also significantly different from each other ($p = 0.01$). Locations are based on postcode centroid at first contact. Axis scales are plotted according to British National Grid co-ordinates of residential postcode at first contact, but the co-ordinates and scale have been removed to preserve sample anonymity.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Social drift may begin earlier in the prodromal phase or expose people to greater socioenvironmental adversities, which increase psychosis proneness.

Limitations

This multilevel study used cross-sectional data to compare social and spatial differences in the three groups in a defined catchment area; we did not have longitudinal data on transition to psychosis in HR participants.

The odds ratios were conservative because, although the control subjects and the population at risk were similar in sociodemographic terms, they came from more densely populated neighbourhoods. The sample of HVs and HR participants was relatively small in this study.

Work package 4: detecting and refining referrals of individuals at high risk for psychosis

Liaison with Education and General practiceS to detect and refine referrals of people with at-risk mental states for psychosis

International efforts to decrease the stigma of psychosis and solicit self- and other referrals have exploited print and television media for public information campaigns, as well as educating members of relevant occupational groups. In this context we compared techniques to identify this important population, ensuring a representative sample of HR individuals for our research and finding a cost-effective way to ascertain this group for EISs to work with subsequently.

We called this initiative LEGS. We employed a cluster randomised approach to finding out which, if any, of two methods of finding HR individuals works best. We targeted those aged 16–35 years registered in and attending primary care (although the intervention will affect a broader age range) and those aged 16+ years in further education in our county. The units randomised (primary care practices and age 16+ educational institutions) in Cambridgeshire and Peterborough were balanced for social deprivation before randomisation using Index of Deprivation scores.[26] We tested whether or not a simple 'postal' campaign, co-ordinated from an office, was more clinically effective and cost-effective than a more elaborate and expensive system of personal liaison by health professionals with the primary care practices and the 16+ educational institutions.

The aim of both interventions was to sensitise staff working in primary care practices and 16+ educational institutions to the nature and likely manifestation(s) of common psychotic symptoms or mental states that put individuals at risk, as defined by existing definitions and established general population screening tools applied in current government epidemiological surveys. Those identified can be referred to their local EIS.

Clinical effectiveness and cost-effectiveness of tailored intensive liaison between primary and secondary care to identify individuals at risk of a first psychotic illness: a cluster randomised controlled trial

The complex educational intervention used in this trial required a number of developmental stages before implementation and evaluation. Here we outline key findings, successes, challenges, limitations and recommendations for future research for each of the stages.

Development of the educational intervention to improve detection of high-risk mental states and first-episode psychosis

A detailed description of this developmental stage has been published (see *Appendix 5*).[27]

First, we investigated what education was required and on what to base our low-intensity intervention (a leaflet sent by post) and the high-intensity, fact-to-face and video package supported by a member of staff. The TPB[15] was selected to guide the design of the educational intervention. Use of the TPB requires the development of a questionnaire to identify and measure specific beliefs associated with each of the theory's constructs: intention, attitude, subjective norm and perceived behavioural control (PBC). The beliefs are then targeted with strategies designed to influence behaviour. Strengthening GPs' intentions to

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

identify individuals at HR was predicted to increase the likelihood that they would identify and refer those at risk.

Research aims

The aim of this stage was to describe the development and psychometric evaluation of a questionnaire designed to identify and measure factors that influence the identification of individuals at HR for psychosis in primary care. This informed the design of the LEGS educational intervention to help GPs and primary care physicians detect these individuals.

Methods for data collection

Following standard TPB guidelines[28] a 106-item preliminary questionnaire was constructed using a semistructured discussion group with eight GPs to elicit commonly held beliefs about identifying HR individuals. The questionnaire was distributed to 400 GPs in 38 practices across 12 counties in England, not including Cambridgeshire and Peterborough where we intended to run the trial.

Analysis

A polytomous graded response model[29] was used to identify redundant items and assess the validity of the questionnaire. Factor analysis was used to assess the structural conformity of the final questionnaire with the TPB. Cronbach's alphas were calculated to determine the reliability of the final questionnaire. Path analysis was conducted to assess the ability of the TPB's constructs to predict intention and reveal the percentage of variance explained by intention.

Key findings

Indirect measures were well constructed and adequately covered the breadth of the measured construct. Items within all direct measures measured the corresponding construct satisfactorily. The alpha values confirmed improvement for each of the constructs in the reduced version of the questionnaire with the exception of intention, which remained the same. The final instrument consisted of 73 items and showed acceptable reliability ($\alpha = 0.77–0.87$) for all direct measures. All of the direct measures of the TPB significantly predicted intention, accounting for 35% of the variance. Subjective norm (perceived professional influences) was the strongest predictor of intention. GPs had positive intentions and attitudes towards identifying individuals at HR for psychosis. The foremost motivational factors for GPs were their perceptions of whether or not other GPs identify HR individuals and whether significant others (e.g. patients, colleagues, health-care system) approved or disapproved of identification.

Successes

Theory underpinned the design of all components of the educational intervention: the understanding of the GPs' behaviour, the development of the measures and the attempt to change behaviour. We confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire to identify GPs' beliefs and intentions concerning the identification of individuals at HR for psychosis.

Theory-based interventions provide an understanding of what works and thus are a basis for developing better theory across different contexts, populations and behaviours. They could, and should, be used more in the NHS where innovation often requires education and behaviour change by staff.

Challenges

The average time taken to complete the questionnaire was 16 minutes. Most of the declining GPs and some of the participating GPs mentioned that the length of the questionnaire was off-putting.

Limitations

The response to the pilot was very low: only 82 (20.5%) GPs returned questionnaires. The cost and time investments were high for such a low return.

Recommendations for future research

The recommendation that an original TPB questionnaire is developed every time a new behaviour is studied,[28] or the same behaviour is studied in a new population, suggests that similar methodology can be used to help GPs in the identification of other pathologies and in a variety of mental health settings. Further application of the TPB in the NHS has already been mentioned.

Design of the educational intervention

Methods for data collection

The information collated from the pilot questionnaire identified specific barriers that we targeted with strategies designed to change clinical practice with respect to identifying HR individuals in primary care.

Key findings

This theory-based information could be important for improving the efficiency of referral pathways and contributing to a reduction in the DUP. We had a clear structure on which to base our low-intensity leaflet intervention and our high-intensity face-to-face and video approaches.

Successes

Mapping theoretical constructs to behaviour change techniques provided a clear framework for process analysis and increased the ability of the intervention to accomplish the desired outcome of motivating GPs to identify individuals at HR.

It was invaluable to have a guide to the different behaviour change techniques, with definitions that addressed different behavioural determinants linked to theoretical constructs. This allowed us to select the most appropriate intervention strategies for GPs.

Challenges

The mapping of theoretical constructs to behaviour change techniques was complex and time-consuming. However, this systematic approach ensured that the behaviour change techniques and delivery methods targeted the theoretical determinants of GPs' behaviour directly.

We learnt from the pilot that individual clinicians have very different levels of knowledge about psychosis and mental health in general. Therefore, it was important to 'pitch' the presentation at the right level so as not to be condescending but at the same time ensure a basic level of understanding. Achieving this balance proved extremely difficult, especially given the time restraints of the 60-minute sessions. Trying to explain the complexities of the at-risk concept in a concise way but also making it educationally appropriate for both GPs and practice nurses took many drafts. Again, it was helpful to have comments from GP colleagues regarding the presentation to guide us before we approved the final version.

Limitations

Ensuring that the leaflet was specific enough to capture all possible at-risk symptoms [attenuated symptoms, family vulnerability and BLIPS (Brief Limited Intermittent Psychotic Symptoms)] without being too sensitive and producing numerous 'false-positive' referrals was a dilemma. Despite utilising many sources of information, including GPs practising outside the trial area, the resulting leaflet proved a little too sensitive.

Recommendations for future research

Few studies have used the TPB to predict intention to take part in an intervention. Such an application could provide valuable information about how best to recruit GPs into future studies.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Implementation of the high-intensity intervention

Successes

The PCRN was useful in terms of accessing surgeries for participation history and informing them about the study. It provided us with the Research Information Sheet for Practices (RISP). The focus of this was provision of information about the practical implications of the research for the participating GPs (What, Where, How often, etc.). This proved more useful than the trial information sheet, which, although detailed and well structured, did not cover enough of the practical details that were required to help practices reach a decision about whether or not to participate.

Having an out-of-area GP review and critique the educational materials proved invaluable for establishing the appropriate pitch and tone and reviewing the content of the intervention.

Three dedicated research and liaison practitioners (RLPs) were specifically recruited for the trial [one man, two women; mean age 45.5 years, standard deviation (SD) 4.7 years]. All were experienced mental health professionals (one psychologist, one nurse, one social worker). They acted as facilitators between secondary and primary mental health services as it is proposed that this is a fundamental role in helping individuals and teams to understand what they need to change and how they need to change it, to translate evidence into practice. Each RLP was responsible for delivering the high-intensity intervention to the surgeries within one of the three geographical areas in Cambridgeshire covered by the trial. The RLPs found that showing empathy (understanding the nature of school/practice life) was central in building a relationship with the teachers/GPs. Face-to-face meetings at the point of consent facilitated this.

A beneficial approach was conveying the research as an important medium through which problems that were relevant for a GP's daily practice could be understood and solutions to the problems could be generated. Flexibility when arranging presentations (i.e. offering more than one session to accommodate all staff) was important for optimising participation.

Convincing the practice leads that participation in the trial would benefit individual GPs, the practice as a whole and most importantly the patients was a key factor in gaining consent to participate in the research. Another successful strategy included emphasising that, by taking part in the trial, GPs could potentially be saving themselves and the practice time because the intervention would allow them to quickly and accurately judge whether or not a young person required a specialist assessment of symptoms. The GPs could see how this would benefit everyone involved.

The GPs were also concerned about what would happen to the individuals who they referred to CAMEO. Assurance that all those identified as being at risk would be invited into the PAATH study for 2 years of mental state monitoring and easy access to a CAMEO psychiatrist if there was any concern about symptoms deteriorating also helped them see the benefits of participating in the trial. We were also able to emphasise that patients without a diagnosis of HR would have a thorough mental health assessment and would then receive appropriate referral on to other services.

Challenges

The trial did not directly involve patients; therefore, it was assumed that only the agreement of practices in the high-intensity arm would be needed for the distribution of leaflets and for their participation in the educational sessions. However, despite discussions with previous members of the Cambridgeshire 1 Research Ethics Committee (REC) about this matter, the committee stipulated that formal consent was required from all invited surgeries, regardless of which arm of the trial they were assigned to. This led to an unexpected long delay in the roll-out of the trial, with contacts, sometimes visits, needing to be arranged with > 100 practices, ultimately resulting in our being granted an 18-month no-cost extension to our programme by the NIHR. The upside was more time to develop the theory-based interventions prior to the trial beginning.

This is a relevant point to place a general comment about our programme. We had to manage challenging situations, a protracted ethical review and subsequent adjustments to our protocol. All of these were ultimately beneficial (see in particular the PAATH study in *Work package 5*), other than the requirement to gain consent from practices to take part in the cRCT. That reduced our sample size but allowed a PAU comparator in those practices that did not consent, and we retained sufficient power to reject our null hypothesis and confirm the hypothesis of doubling referrals with uncanny accuracy. In retrospect, we would have benefited from a Programme Steering Group as is now required by the NIHR, but we drew on valuable advice from the Central Commissioning Facility and from the late Professor Helen Lester, who inspired some of our programme and was generous with her advice.

The recruitment process was lengthy and at times extremely frustrating. Busy GPs were difficult to contact directly but practice managers were good liaison intermediaries. However, many of the practice managers were very protective of the GPs' time and were occasionally more negative about the likelihood of the practice participating than were the GPs when we eventually spoke to them. It took many attempts to persuade some practice managers to facilitate discussion of the research trial at team meetings, despite the fact that information had already been sent to the lead GPs within the practices.

The time commitment required to participate in the trial was a key issue for GPs. Reassurance that participation involved essentially just the 2 hours of educational sessions over the whole 2 years of the trial, for which the practice would receive income, was helpful in motivating them to participate.

Recommendations for future research

As has become evident in much health research, the process of ethical review can be protracted and frustrating for researchers. GPs' negative attitudes, concerns and ambivalent feelings should be elicited and addressed with recruitment strategies.

We relied on the assumption that lead GPs would read the trial information sheet, discuss it with their colleagues and decide whether or not they wanted to participate. It became apparent during the trial that this was not always the case, as many GPs with other demands on their time did not know about our trial. A more advantageous approach could be to advertise the trial with individual GPs prior to gaining consent.

Implementation of the Liaison with Education and General practiceS cluster randomised controlled trial with general practices

The full protocol for this trial has been published.[30]

Research aims

Our main aim was to test the null hypothesis that, in terms of the effectiveness and cost-effectiveness of detecting individuals at HR aged 16–35 years, a theory-based educational intervention for primary care was not different from a postal information campaign co-ordinated from an office in a secondary care-based EIS (CAMEO). The journal, *Trials*, where we published the protocol, insisted on this null construction, which is not easy to follow.

Formulated in a positive manner, this cRCT compared two different approaches to liaising with primary care to increase detection and early referral of people at HR to a specialist early-intervention team for young people with psychosis. We predicated the sample size and power on a doubling of HR and FEP referrals by the high-intensity intervention.

Methods for data collection

General practices were randomly allocated into two groups to establish which is the most effective and cost-effective way to identify people at HR for psychosis. One group received postal information about the local EIS, including how to identify young people who may be in the early stages of a psychotic illness. The second group received the same information plus an additional ongoing theory-based educational intervention with dedicated liaison practitioners to train clinical staff at each site.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The primary outcome was count data per practice site on the number of HR referrals to a county-wide specialist EIS (CAMEO). This was conducted over a 2-year period. All referrals during the duration of the trial were assessed clinically by the study team and stratified into those who met criteria for HR or FEP according to the CAARMS[11] (true positives) and those who did not fulfil such criteria (false positives).

Analysis of the effectiveness of the intervention

Given that the main outcome (referrals per practice) was count data, the yield, our primary statistical approach was Poisson regression. Results were adjusted for surgery size and the number of GPs working in each site was considered as a covariate in the model. We also employed Pearson's chi-squared test and Fisher's exact test to compare demographic characteristics of the general practices. All of the analyses were performed using the statistical package R (version 3.0.0; the R Foundation for Statistical Computing, Vienna, Austria).

Analysis of the cost-effectiveness of the intervention

Decision-analytic modelling was used to investigate the cost-effectiveness of the high- and low-intensity interventions compared with PAU. A decision tree was constructed in Microsoft Excel 2013 to model the care pathways of the young people in the trial and assess the costs and effects over 2 years associated with the two active interventions and PAU. The costs of (a) the high- and low-intensity interventions, (b) diagnosing referrals who did not meet criteria for HR or FEP (false positives), (c) diagnosing and treating identified HR and FEP cases (true positives) and (d) the subsequent treatment of HR and FEP cases who were not identified (false negatives) were included.

Results of the Liaison with Education and General practiceS cluster randomised controlled trial

The results from this trial have been published online (see *Appendix 7*).[31]

Key findings on the effectiveness of the intervention

The intervention succeeded in raising awareness of potential psychotic symptoms. Between 22 December 2009 and 7 September 2010, 54 of 104 eligible practices provided consent and between 16 February 2010 and 11 February 2011 these practices were randomly allocated to the interventions (28 to the low-intensity intervention and 26 to the high-intensity intervention); the remaining 50 practices constituted the PAU group. Two high-intensity practices were excluded from the analysis. In the 2-year intervention period, high-intensity practices referred more FEP cases than low-intensity practices [mean (SD) 1.25 (1.2) for high intensity vs. 0.7 (0.9)] for low intensity; IRR 1.9, 95% CI 1.05 to 3.4; $p = 0.04$], although the difference was not statistically significant for individuals at HR of psychosis [mean (SD) 0.9 (1.0) for high intensity vs. 0.5 (1.0) for low intensity; IRR 2.2, 95% CI 0.9 to 5.1; $p = 0.08$]. For HR and FEP cases combined, high-intensity practices referred both more true-positive [mean (SD) 2.2 (1.7) for high intensity vs. 1.1 (1.7) for low intensity; IRR 2.0, 95% CI 1.1 to 3.6; $p = 0.02$] and more false-positive [mean (SD) 2.3 (2.4) for high intensity vs. 0.9 (1.2) for low intensity; IRR 2.6, 95% CI 1.3 to 5.0; $p = 0.005$] cases. Most of these (68%) were referred on to appropriate services. Referral patterns did not differ between low-intensity and PAU practices (*Figure 6*).

Key findings on the cost-effectiveness of the intervention

Details of the quantitative economic results and how this part of the trial was conducted can be found at www.thelancet.com/cms/attachment/2035390784/2050868157/mmc1.pdf (accessed 19 January 2016).

Total cost per true-positive referral in the 2-year follow-up was £26,785 in high-intensity practices, £27,840 in low-intensity practices and £30,007 in PAU practices. The lower cost was attributable to fewer false negatives (HR and FEP cases that are not identified), which are assumed to be associated with treatment costs at a later point. The high-intensity intervention was the most cost-effective strategy.

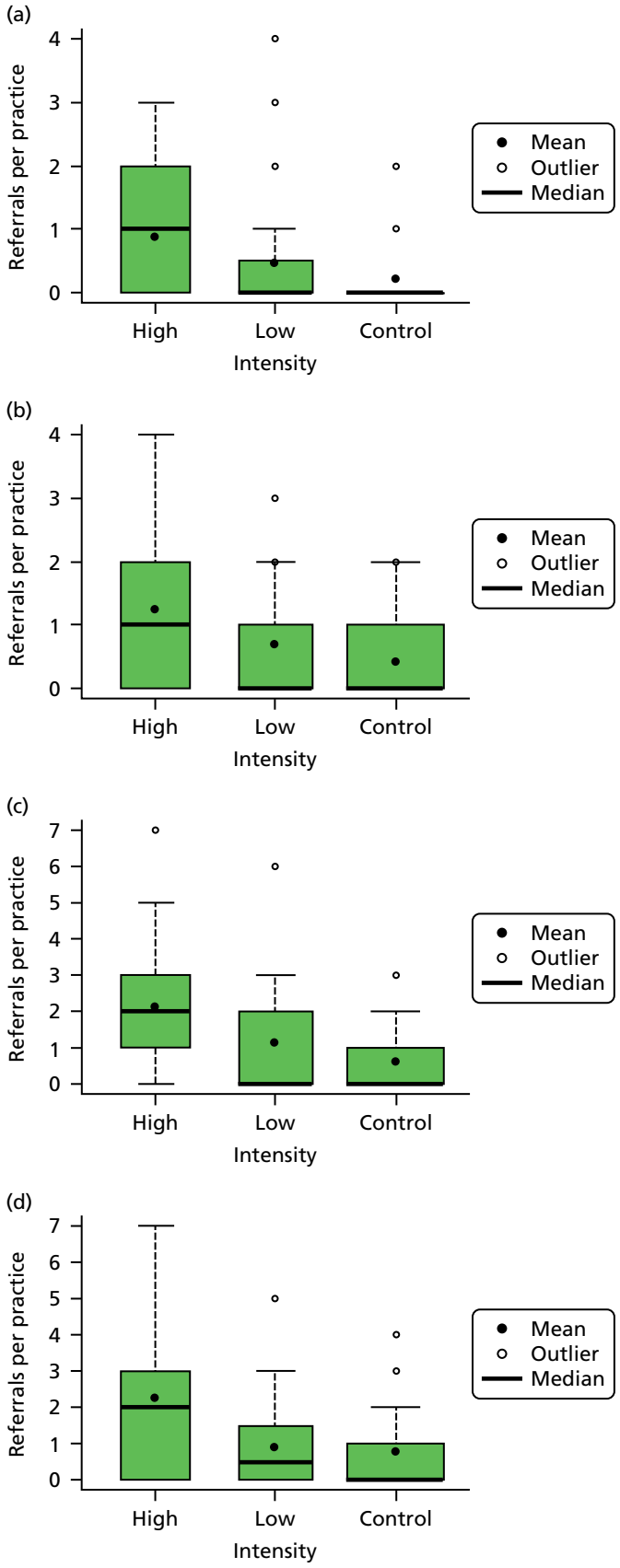


FIGURE 6 Comparison of the distribution of referrals by intervention group. (a) HR; (b) FEP; (c) true positives; and (d) false positives. Lower hinge = 25th centile; upper hinge = 75th centile; line = median; filled dots = means; open dots = outliers.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Interpretation

This intensive intervention to improve liaison between primary and secondary care for people with early signs of psychosis was clinically effective and cost-effective. Increasing the resources aimed at managing the primary–secondary care interface provides clinical and economic value in this setting.

Successes

In the south of the county, mental health services were cohesive and the early-intervention team was well established. Generally speaking, the GPs in the south of the county were much better informed about the CAMEO team and what it could offer patients. As a result, they were more open to participating in research connected to psychosis.

The GPs were willing to discuss their patients in detail with each other at the two educational sessions. As a general rule, the GPs responded well to the facts and figures used to illustrate the main points within both the presentations and the DVD. Comments were made about how useful the DVD would be for training GPs and disseminating the information to colleagues who were unable to attend the presentations. As a 'continuing professional development' session, many of the GPs and practice nurses were positive about the educational intervention that they attended.

Notably, as with PsyMaptic (see *Work package 3*), NHS England is currently using these results in its strategy to implement waiting time standards and targets for EISs nationally.

Challenges

General practitioners' perceptions of the poor relationships between primary care and secondary mental health services was a barrier to participation and the building of relationships with the RLPs. In the north of the county, EISs were relatively new and historically there had been difficult relationships between primary care and local mental health services. Attitudes in the north of the county towards the liaison aspect of the trial and the potential outcome of referrals to CAMEO were rather negative in comparison with attitudes in the south. During some of the educational interventions, several GPs were quite adversarial and extremely critical of mental health services in general. However, the process of the study appeared to help this and the GPs had, after all, agreed to take part.

It took GPs between 15 and 30 minutes to complete the TPB questionnaire. Many of them found it arduous and complained that it was too lengthy. The RLPs had to work hard to justify the displeasure that some of the GPs felt at having to complete such a long questionnaire. Much effort was made to explain why such a questionnaire was being used and how much of an essential part of the research it was. However, this remained the most consistent criticism of the interventions delivered.

During the 60-minute sessions it was a challenge to deliver the presentation, complete questionnaires and leave some time for questions at the end. Some GPs were very keen to discuss particular patients, whether or not they had HR symptoms. The numbers of clinicians who did attend the sessions was always fewer than the numbers practising at the individual surgeries.

During the first educational intervention, some GPs commented that they had not seen any patients with suspected HR symptoms since receiving the leaflet and were rather dismissive of how relevant this all was to their everyday experiences of young people and their problems. To address this, the importance of identifying the early signs of psychosis was emphasised in the DVD by the chief investigator of the trial, Professor P Jones, Head of Psychiatry at Cambridge University. He used the example of 'crushing chest pain' as an analogy for the importance and urgency of identifying and treating psychotic symptoms because of the devastating, long-term effects of untreated psychosis on the individual. This aspect of the DVD did generate discussion with some groups of GPs and provided an opportunity to emphasise again how the long-term effects of a psychotic illness should be avoided at all costs.

To facilitate further reinforcement of the symptoms that GPs should be looking for in young people, practices in the high-intensity group were given specific details about the symptoms of the HR patients who they referred. These were provided in the initial assessment feedback document and in the updates for each of the follow-up assessments. GPs rarely commented on this more detailed feedback during the second educational intervention.

There were mixed responses to the DVD. Some GPs found it very helpful; however, some found it to be repetitive because of similar material in the 'revision' presentation.

Limitations

A variety of reasons were given for non-attendance at the sessions. These ranged from being on duty to sickness or being on annual leave. Our strategy to address this was to offer practices multiple visits. This facilitated the maximum number of clinicians attending each session. At some surgeries GPs could not stay for the whole session because of clinical commitments; therefore, it is possible that some GPs missed vital information. Another consequence was that not all of the surgeries had a comparable educational experience and this could have had some effect on the results of the trial. We used an intention-to-treat approach for the analysis.

General practitioners rarely telephoned RLPs to discuss particular patients or symptoms, despite being encouraged to do so at every opportunity during the course of the trial. We suspect that their decisions to refer did not depend on the minutiae and finer points of psychopathology that interest secondary mental health care. If the number of RLPs was scaled down or RLPs were removed from the high-intensity intervention it could have been more cost-effective; however, this is conjecture.

Sufficient copies of the laminated version of the leaflet were sent to each practice that each GP could receive his or her own copy before the date of the intervention. When we asked the GPs about their experiences of using the leaflet it was rather disappointing to discover that many of them had not used it and in some practices had not seen it at all. In some cases this seemed to be an administrative error; the leaflets may have arrived at the practice but had not been distributed to the individual GPs. Some of the lead GPs took responsibility for this; in other practices it was the responsibility of the practice manager. Clearly, in some cases our leaflets remained in the postal noise, not being recognised as signal.

Recommendations for future research

Many of the GPs were doubtful about being able to refer accurately. They considered that many of the signs and symptoms that could indicate risk are also present in other mental health illnesses such as anxiety, depression or obsessive–compulsive disorder. This issue was revealed in the pilot study; therefore, we had focused on encouraging the GPs to keep their 'HR radar' on when interviewing a young person. We specified that they should use the leaflet to help them ask the relevant 'probing' questions, which would guide their referral practice. Their lack of confidence, despite these strategies, is an issue that needs to be addressed in future research.

During the course of the trial many GPs expressed that (1) they would rather have had an electronic version of the leaflet or (2) specific at-risk symptoms should have been included in their nationwide, web-based illness identification tool, which is available to all GPs. This would have been a good idea.

The trial did not measure how long the intervention effect endures or calculate the optimal number of sessions required. This information is important to enable a balance between intervention effectiveness and cost-effectiveness while maintaining identification of HR and FEP individuals.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The Liaison with Education and General practiceS cluster randomised controlled trial: liaison with 16+ educational institutions to detect and refine referrals of people with at-risk mental-states for psychosis

The aims, methods for data collection and analyses for the cRCT with 16+ educational institutions replicated the work with primary care practices but in a different setting. Briefly, we used the TPB to assess teachers' baseline knowledge and motivation to change behaviour regarding pupils with HR mental states. We developed a low-intensity intervention and a high-intensity 'teach the teachers' intervention that we compared in a cRCT.

In our programme we made the primary care trial the priority and, because of disappointing initial results in the educational setting, have completed this educational work later. The follow-up period for counting referrals has now come to an end and we are analysing the data. Here, we outline key findings, successes, challenges, limitations and recommendations for future research for each of the completed stages.

A detailed description of this developmental stage has been published (see *Appendix 8*).[32]

Development of the educational intervention

Methods for data collection

An elicitation phase revealed beliefs underlying teachers' motivations to detect HR students and informed the construction of a preliminary 114-item questionnaire incorporating all constructs outlined in the TPB. To define the determinants of teachers' intention to identify HR students, 75 teachers from secondary and further education institutions in 12 counties surrounding Cambridgeshire completed the questionnaire. A psychometric model of item response theory was used to identify redundant items and produce a reduced questionnaire of 44 items that would be acceptable to teachers.

Analysis

A psychometric evaluation of the questionnaire was conducted. The polytomous graded response model was used to examine the validity items within direct and indirect measures and to inform decisions regarding the removal of items. Cronbach's alpha coefficient was used to assess the internal consistency of the direct measures of attitude, subjective norm and PBC. The relationship between intention and the indirect and direct measures was investigated using path analysis.

Key findings

The average time taken to complete the TPB questionnaire was 20 minutes. The majority of the teachers (63%) reported never having attended any kind of mental health training during their careers.

Indirect measures were well constructed and adequately covered the breadth of the measured construct with the exception of PBC. Items within all direct measures measured the corresponding construct satisfactorily. Only one item within direct subjective norms, direct PBC, showed a factor validity of < 0.5. Cronbach's alphas for the reduced questionnaire showed acceptable internal consistency.

Perceived behavioural control was the strongest predictor of intention, followed by attitude. Subjective norm did not predict intention. Collectively, the direct measures explained 37% of the variance of intention to identify HR for psychosis. Mean scores for direct measures were just above the mid-scale score for intention and attitude and just below the mid-scale score for subjective norm and PBC.

Teachers considered identifying students at HR for psychosis a worthwhile behaviour and would attempt identification during the school day and believed that their peers or superiors might not approve of them identifying at-risk students. The greatest source of social pressure came from the senior management team within 16+ educational institutions. Teachers' confidence and control over identification were low.

Increasing awareness and understanding of mental health issues emerged as the most important source of personal positive beliefs. The lack of access to information, knowlege and resources could hinder teachers' identification behaviour. Teachers' perceptions of how confident they are that they are capable of identification and how much control they have over identification were prominent motivational factors.

Our questionnaire proved to be reliable, with the analysis supporting the predictive power of intention within the TPB model.

Successes

We have confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire to identify teachers' beliefs and intentions concerning the identification of individuals at HR of psychosis.

Limitations

Despite strenuous efforts, the response rate to our questionnaire was very low: only 75 teachers (9.5%) returned the questionnaire of the 793 invited. External validity could have been undermined if respondents differed systematically from non-respondents, which they probably did. The potential limitations of using self-report measures must be considered when interpreting the results as acquiescence and social desirability may have been influencing factors.

Recommendations for future research

Objective measures of behaviour should be incorporated in future research to avoid reliance on self-report.

The questionnaire length would be a limiting factor for TPB studies with teachers; therefore, options for reducing the number of items should be explored in future research.

Design of the educational intervention

Successes

Work with 'consultant' teachers from outside the trial area was very important so that the language used about symptoms could be assessed and deemed to be at an appropriate level for non-medical staff.

Challenges

Teaching teachers was quite a daunting prospect for the RLPs. Achieving the balance between an appropriately academic language for a group of professional teachers and recognising that many teachers would have very little or no knowledge at all about psychosis required many revisions of the presentation material. Describing psychosis and HR symptoms had to be approached differently for the teaching staff as they had no clinical knowledge. Success in presenting this kind of intervention required the open acknowledgement of differing levels of knowledge and understanding about mental health problems. As both nurses and teaching staff would be present at the educational sessions, the needs of these two different professional roles needed to be addressed within the presentations.

It was important not to present the material as all encompassing but rather as an introduction to the subject, covering all of the essential information. Therefore, further information was made available through a recommended reading list, references and a paper copy of the presentation. This material was included in packs that were distributed at the end of the presentations.

Teachers were not able to refer directly to a secondary mental health team but had to refer through school and college nursing staff. It was necessary to contact the nurses' local area team prior to the roll-out of the intervention to ensure that the referral procedure was in accordance with existing referral practices. This also prepared the nursing staff for the possible increase in number of referrals. Each individual institution's referral procedures were respected, rather than dictating a county-wide protocol for the study.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

It was also necessary to stress the importance of discussing any referral with the student, to establish that consent had been given for information sharing.

Implementation of the high-intensity intervention

Successes

The consent visit to 16+ educational institutions to discuss the trial seemed to considerably improve awareness of the EIS and the importance of not missing what could be the signs and symptoms of a developing mental illness in students who were not performing to expected levels. At the initial contact with 16+ educational institutions the response from most of the head teachers was extremely positive. The majority could see the importance of identifying students early to prevent serious illness from developing.

Many of the teachers were interested in the content of the presentations, asking pertinent questions. Positive recurring themes were:

- the opportunity to discuss students who they recognised could be HR cases
- a genuine enlightenment by the discussion of symptoms
- awareness, for the first time, that there is a service that specialises in the assessment and treatment of young people with psychosis.

The nurses and pastoral support staff felt more confident when talking to students because of the leaflet and what they had learnt from the presentations.

Challenges

As stated in the previous section, many of the teachers were interested in the content of the presentations, asking pertinent questions. Negative recurring themes, that are themselves findings, included:

- the teachers held strong views that identifying HR symptoms in students was not part of a teacher's role
- a reluctance to take on this extra 'pastoral' responsibility
- a feeling that the content of the presentations was too medical and health related
- a level of genuine anxiety about whether or not they should even attempt to identify HR symptoms.

Attempting to speak to the head teachers of some 16+ educational institutions proved difficult, with one school telling us that 'we don't have that kind of problem in this school!' Conversely, other head teachers expressed an eagerness to be in the high-intensity group so that their staff could receive the high-intensity intervention. Many of the head teachers had not heard of the CAMEO service although others had through previous experience of having one or two students with psychotic disorders in their college.

Head teachers expressed a desire to have a 'youth-focused' service to which to refer students when necessary. Therefore, it was necessary to stress that referrals would be appropriate only for those who may be at risk of developing psychosis, not for those with any mental health problems generally. Having said that, our primary care trial suggests that this course of action may have benefits.

It became apparent that there were going to be few opportunities within the timetables of 16+ educational institutions to allow staff to be present all together for the presentations. The RLPs were able to reassure the head teachers that they could be as flexible as required to deliver the intervention. Solutions included delivering the intervention out of teaching hours or during lunch breaks or having the option of multiple sessions (one of the interventions was delivered at 0830 in the morning to accommodate as many teachers as possible).

Distributing and collecting the questionnaires at the educational sessions was challenging as the groups consisted of up to 50 teachers. At some of the larger groups extra research staff helped to facilitate this aspect of the presentations.

These larger numbers also meant that waiting for all of the teachers to complete the questionnaire became a problem, with small groups of teachers chatting among themselves before the rest had finished. This became quite disruptive and it took some time to retrieve the attention of those attending in order to continue with the second part of the presentation. Completing the questionnaire elicited some protesting, but it was stressed that this was very much a part of the research and essential to measuring the change in referral behaviour before and after the interventions.

Many teachers raised the subject of substance misuse-related psychosis. They were interested to know whether or not the use of substances would increase the likelihood of psychotic symptoms and whether or not this would be an exclusion criterion for referral to CAMEO. We reassured them that students who may have symptoms following alcohol or substance use should not be excluded from referral for assessment by CAMEO.

Limitations

There were several hundred teachers at some of the colleges and this made it almost impossible to know whether or not the leaflets had been distributed effectively to all staff. It is possible that a proportion of the teaching staff did not see, or have regular access to, the leaflet.

Recommendations for future research

Leaflet distribution should be monitored and verified in future interventions with 16+ educational institutions. Identifying and fitting in research with the rhythm of teachers' professional development (e.g. 'Baker days') would be useful. That said, as with the GPs, teachers' time is increasingly pressured and so finding innovative ways to generate research-based knowledge is a challenge.

We have completed the collection of data from the teachers involved in the LEGS trial. We plan to analyse these data over the next 6 months.

Supplement to the original research proposal: the Prospective Analysis of At-risk mental states and Transitions into psycHosis study

Rationale

The original design of the LEGS trial was to assess all referrals generated by the surgeries and schools in all three arms. These young people have often remained under GPs caseloads or unidentified in schools, with likely deterioration of functioning and academic tasks because of non-specific symptoms of psychosis. The individuals who were identified as HR would be offered 3-monthly follow-ups to assess their progress and monitor any transitions to FEP. Depending on the level of severity and particular needs, true HR cases would also be offered 'signposting' to appropriate teams. Non-true HR cases would also be discussed and referred to more appropriate mental health teams according to symptoms and needs. However, the Cambridgeshire 1 REC granted approval on the basis that the liaison with primary care and educational institutions and follow-up of ensuing referrals was divided into separate studies. This resulted in the design of the PAATH study. This was used to enhance the programme. This new work package, created as a result of a decision by an ethics committee, was added to the programme and represented a remarkable enhancement of the original grant application through an efficient use of available resources. We present it as work package 5.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Work package 5: follow-up of referrals of individuals identified as being at high risk for psychosis

The Prospective Analysis of At-risk mental states and Transitions into psycHosis

Research aims

The first aim of this study was to establish the prevalence of transition from HR mental states into FEP. We then aimed to describe and compare the characteristics of people with HR mental states who transitioned into FEP and the characteristics of those who did not. This would facilitate effective responses with better assessments and more focused interventions. Secondary objectives included various epidemiological and clinical analyses that would (1) contribute to an enhanced delineation of people at HR who are more likely to develop a full psychotic illness and (2) allow comparisons between people at HR and HVs, especially with regard to possible causal factors tied to sociodemographic and comorbid clinical characteristics, substance use and trauma history. Finally, we aimed to describe the morbidity and the effect on social functioning and quality of life of HR states, which are sometimes seen by services as merely predictors of FEP rather than as highly troublesome mental health conditions themselves.

Methods for data collection

All individuals at HR for psychosis living and detected in Cambridgeshire and Peterborough, including those identified by GPs or 16+ educational institutions in the LEGS cRCT, were offered a systematic follow-up in the context of this prospective, naturalistic study. Participants between the ages of 16 and 35 years were referred to our offices through a number of different routes (GPs, schools, relatives, friends). Candidates were initially assessed by both a psychiatrist and an experienced non-medical clinician trained in the CAARMS questionnaire,[11] which is used to detect individuals at HR for psychosis. This was already routine practice in the CAMEO EIS. Individuals who met criteria for HR were invited to take part in the study and written consent was obtained.

A total of 60 help-seeking HR participants were followed up for 2 years from the initial referral date. Interestingly, all help-seeking HR individuals referred to us were willing to be followed up in the context of this study. However, as stated below, we encountered difficulties in retaining some of them for the whole follow-up period. During this period they were asked to attend nine interviews (at baseline and then every 3 months until the end of the study) at which they completed structured interviews and questionnaires under the direction of a clinical researcher. These questionnaires targeted different domains such as sociodemographic characteristics, diagnosis, psychiatric morbidity, trauma history, substance use and functioning, among others. The interviews took place in our CAMEO offices in Cambridge and Peterborough, at GP practices or in participants' homes.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

A random sample of 60 HVs matched for age (16–35 years), sex and geographical location was recruited by using the Postcode Address File® (PAF) provided by the Royal Mail. Addresses within the same three-digit postcodes as those of cases were picked at random and sent a letter inviting residents aged 16–35 years to participate. This methodology for finding comparison subjects had been successfully used in the ÆSOP study.[6]

Healthy volunteers underwent the same battery of questionnaires at baseline, 1 year and the end of the follow-up period unless they were, themselves, diagnosed as HR. In this case they would be offered the same number of interviews, questionnaires and possible clinical interventions as the HR individuals. HVs were offered £50 as a reward for taking part in the study and an incentive of £50 if they completed the interviews. *Table 3* provides a sociodemographic comparison between HR and HV participants in the PAATH study.

TABLE 3 Sociodemographic comparison between HR and HV participants in the PAATH study

Sociodemographic characteristics	HR participants ($n = 60$)	HVs ($n = 60$)	*p*-value
Age at study entry (years), median (min., max., SD)	19.89 (16.41, 30.21, 2.38)	22.60 (16.18, 35.57, 5.68)	< 0.001[a]
Sex, *n* (%)			
Male	31 (51.7)	26 (43.3)	0.465[b]
Female	29 (48.3)	34 (56.7)	0.465[b]
Ethnicity, *n* (%)[c]			
White	56 (93.3)	55 (91.7)	1.000[b]
Mixed	2 (3.3)	2 (3.3)	1.000[b]
Asian	1 (1.7)	2 (3.3)	1.000[b]
Black	1 (1.7)	1 (1.7)	1.000[b]
Occupational status, *n* (%)[d] ($n = 7$ with missing data)			
Unemployed	20 (33.3)	8 (13.3)	0.004[b]
Employed	8 (13.3)	27 (45.0)	0.001[b]
Students	25 (41.7)	25 (41.7)	0.575[b]

max., maximum; min., minimum.
a *t*-test.
b Fisher's exact test.
c 'White ethnicity' refers to subjects who are white British, white Irish or of another white background; 'mixed ethnicity' refers to those who are mixed white and black Caribbean, mixed white and Black African, mixed white and Asian or of any other mixed background; 'Asian ethnicity' refers to those who are Indian or Chinese; 'black ethnicity' refers to those from any black background.
d Occupational status is broadly categorised into three groups: 'unemployed' includes subjects who do not have a job – they are looking for work or not looking for work (e.g. housewife) or are not able to work for medical reasons; 'employed' refers to people who have full-/part-time employment or who are employed but currently are unable to work; 'students' refers to full-/part-time students including those who are also working some hours.

Challenges of the Prospective Analysis of At-risk mental states and Transitions into psycHosis study

The process of identifying participants

Young people referred to and assessed by CAMEO but who were not experiencing a FEP were offered a follow-up interview including an assessment using the CAARMS to confirm or refute whether or not they met the criteria for HR for psychosis. Those who met the criteria were invited to another interview at which the outcome of their assessment was explained and they were provided with information about participation in the PAATH study. The study was explained in detail, drawing attention to the fact that there would be no treatment or intervention. It was also explained that participants would be seen over a period of 24 months, once every 3 months, undergoing mental state monitoring in the form of a selection of psychometric tools. It was difficult to describe the required involvement without sounding as though the participants were being asked to give up their time for no obvious advantage or direct therapeutic benefit. No payment was offered to participants but it was explained that by participating in the research they would have their symptoms monitored very carefully. Should the symptoms worsen they could be seen promptly by the psychiatrist leading the research. This provided some incentive because they would be seen much sooner without having to go through the usual route of referral by their GP back into secondary services.

Participant attrition

We implemented a variety of strategies to retain participant involvement in the PAATH study. Despite achieving a good rapport with many of the participants, keeping in touch with them after the baseline session and encouraging them to continue the 3-monthly assessment sessions was a real challenge. This was probably in part because they were generally a mobile, transient young population.

Lack of clinical follow-up by mental health services

Although a high proportion of those meeting the criteria for HR were signposted on to other services for support [e.g. Improving Access to Psychological Therapies (IAPT) service or locality mental health teams], some participants did not engage with the other service at the outset or soon dropped out. Therefore, members of the research team may have been the only mental health professionals seeing the young person. We implemented protocols to take clinical risk issues into account. Clear guidelines were followed, should any clinical crisis occur. However, because the CAMEO team is not funded to work with HR individuals it did create confusion with regard to clinical responsibility. Other mental health teams could mistakenly believe the participant to be under the care of the CAMEO team rather than participating solely in a research study, despite our best efforts to make it very clear in our clinical documentation that this was not the case. Some PAATH participants would inform other mental health professionals that they were ‘under CAMEO’, erroneously giving the impression that they were being treated, without understanding the confusion that this created. To try and solve this potential confusion, we sent a clear explanation of the situation of the participants with regard to clinical responsibility to any mental health professionals involved and to the participants’ GPs. Standard letters were sent out to the referrers or to our clinical colleagues in other secondary care teams as appropriate.

Respondent fatigue

At baseline and thereafter at 6-monthly intervals a batch of 10 assessment tools was administered to each participant. This process took approximately 2 hours for each participant. It was difficult at times to keep the participants engaged with such a lengthy session. Several of the assessment tools contained similar questions despite assessing different aspects of the participants’ mental health and this caused frustration for the participants. Moreover, several of the tools themselves were lengthy, especially some of the self-completing assessments. At times, much encouragement and support was required to ensure that participants completed all of the assessments. We always tried to complete the whole batch in one session to prevent the possibility that participants would drop out, resulting in missing data.

© Queen’s Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

The potential therapeutic effect of monitoring

It was inevitable that working relationships would be formed between the participants and the research clinicians during the months of assessment. Seeing someone every 3 months for 2 years resulted in significant monitoring of their mental health. This resulted in a certain amount of understanding of their current situation and any issues or difficulties that they were having in their lives. Although no overt or deliberate therapeutic intervention was provided, the continuity of contact and necessary interest in the participants' well-being resulted in a relationship that it could be argued was therapeutic in itself and this may have influenced the course of the participants' illness to some degree.

For the researchers it became increasingly frustrating that we were seeing many young people for whom there was no appropriate service available. Services are still divided between child and adolescent and adult mental health teams. Therefore, young people have no access to a service that provides specialist, non-stigmatising and youth-friendly approaches to working with mental health problems in young adults.

Referrals to Improving Access to Psychological Therapies in primary care

The majority of young HR individuals that we evaluated and followed up over the course of our programme indicated a strong preference to be treated in primary care rather than in a specialist mental health service. Interestingly, during our programme the NHS implemented in primary care one of the most important innovations in mental health services in recent decades: the IAPT programme [see www.iapt.nhs.uk (accessed 19 January 2016)]. This programme massively increased access to psychological treatments for anxiety and depression in primary care across England, promoting the use of talking therapies based on cognitive–behavioural therapy (CBT) approved by the National Institute for Health and Care Excellence (NICE).

Given the high prevalence of depression and anxiety in the HR individuals assessed in our services, we made a number of referrals ($n = 66$) to IAPT services. Many of them ($n = 22$; 33%) were not accepted because IAPT therapists were not appropriately trained to provide psychological therapies to people experiencing psychotic-like experiences, even if these were in the context of depression and anxiety. Of those who were accepted ($n = 44$; 67%) for treatment by IAPT services, a significant proportion ($n = 25$; 57%) disengaged after one or two therapy sessions. This uncovered the need to tailor IAPT CBT to engage and treat individuals with these clinical presentations, enhancing engagement, assessment of complex problems and management of psychotic-like experiences by de-catastrophising and normalising, as also recommended in NICE guidelines for schizophrenia.[33]

Prevalence of transition from high risk to first-episode psychosis over 2 years

Key findings

Only three out of 60 (5%) of our HR sample made a full transition to a psychotic disorder based on structured clinical diagnosis (10% when CAARMS[11] criteria were employed) over the 2-year follow-up period. This was an unexpectedly low figure given our prior beliefs at the beginning of the programme in 2008, but is in line with the results of other studies published over recent years, including the Early Detection and Intervention Evaluation for people at risk of psychosis (EDIE-Two) study,[7] a RCT of CBT for young people with HR mental states in which we were a study site. Overall, the transition in the intervention and control groups was < 10%. This is a really important finding for young people with HR mental states – they are not at very HR of transition to a FEP over 2 years and the term 'high risk' is almost a misnomer. Rather, services can focus on the mental health problems that they have in addition to their psychotic experiences, largely depression and anxiety (see *Psychiatric morbidity in the high-risk sample*).

Thus, it is important not only to pay attention to the evolution of HR individuals but also to thoroughly understand the type and severity of the psychopathology and the psychological and demographic characteristics of these presentations as an independent morbid population cluster. The development of specific care pathways or beneficial interventions for this population is urgently required.

Strengths

The epidemiologically principled design, the standardised assessment with the CAARMS[11] and the 2-year follow-up are particular strengths of this study.

Limitations

The study is relatively small with low precision in the prevalence of transitions to FEP. Recruiting a sample large enough to lead to a step change in power and precision (e.g. 10 times as many) would be a huge challenge requiring multicentre working. Participation in the PAATH study could indirectly involve the provision of non-specific clinical care. One-to-one sessions with a supportive research clinician every 3 months could reduce stress and subsequently the likelihood of conversion into frank psychotic disorders. This may have reduced the number of transitions.

Recommendations for future research

The inclusion of a follow-up component in future research in this area with a more sophisticated approach to outcome than merely HR, FEP or normal is recommended. These states all have a wide range of expression, with a kaleidoscopic variability over the medium term in some people. Studies equipped to capture this would allow the relationships between psychotic experiences and other psychopathology to be more clearly understood and more effective management to be devised.

Psychiatric morbidity in the high-risk sample

See *Appendix 9* for the published report of this work.[34]

Research aims

To ensure that appropriate care pathways and interventions are put in place that benefit people at HR for psychosis, the type and severity of psychopathology in this group must be understood. The aims of this study were to describe the clinical and functional characteristics of young people at HR for psychosis. We compared their level of global functioning, occupational status and quality of life with those of a sample of HVs recruited from the same geographical area.

Methods for data collection

We collected sociodemographic information, clinical morbidity measures including the Positive and Negative Syndrome Scale (PANSS),[35] the Beck Depression Inventory version II (BDI-II),[36] the Beck Anxiety Inventory (BAI),[37] the Young Mania Rating Scale (YMRS)[38] and the Yale–Brown Obsessive Compulsive Scale (YBOCS),[39] functioning measures including the Global Assessment of Functioning (GAF)[40] and occupational status, as well as subjective quality of life measured by the Manchester Short Assessment of Quality of Life (MANSA)[41] for 60 HR individuals and 45 HVs. Although the final sample total for the HV group in the PAATH study was 60, this paper was published before recruitment was complete; therefore, the HV sample includes only 45 participants.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Analysis

All comparisons were made using the chi-squared test or Fisher's exact test for categorical variables and the *t*-test or Mann–Whitney *U*-test for continuous variables.

Key findings

Individuals at HR are a heterogeneous group with members commonly having more than one psychiatric disorder, mainly depression and/or anxiety or anxiety-related states such as obsessive–compulsive disorder. In contrast with previous cohorts, individuals at clinical HR in our sample were affected by mild psychotic symptoms. In addition to psychotic symptoms, a wide range of serious psychiatric disorders, suicidal ideation/intention, depressive and anxiety symptoms, low levels of quality of life and employment status impede the global functioning of those at HR.

High-risk individuals had poorer functioning with significantly lower GAF scores for symptoms and disability than HVs (both $p < 0.001$). There was a statistically significant higher prevalence of moderate/severe depression ($p < 0.001$ and $p = 0.025$, respectively), anxiety ($p < 0.001$), obsessive–compulsive behaviours ($p < 0.001$) and suicidality ($p < 0.001$) in HR individuals than in HVs. Therefore, a HR mental state may be associated not only with an increased risk for psychosis but also other psychiatric disorders (*Table 4*). Indeed, linked psychometric analyses by the authors (JS, JP, TJC and PBJ) in other population samples indicated that psychotic experiences measure the severe end of a common mental distress factor, which is consistent with these results.[42]

This prominently poor global functioning and quality of life (*Table 5*) combined with a significant risk of suicidality justifies special attention from mental health services to develop appropriate care pathways.

Limitations

A chronicity criterion should have been used to determine any differences in psychopathological profiles between individuals with longer and shorter durations of HR symptoms.

The study was cross-sectional and therefore it was not possible to identify causal relationships between the HR state, psychiatric morbidity and impaired functioning.

Recommendations for future research

Rather than exclusively focusing on the treatment and/or prevention of psychosis, clinical interventions with individuals at HR identified in EISs should aim at targeting a broader range of psychopathology, especially mood and anxiety symptoms.

TABLE 4 Clinical comparison between HR individuals and HVs in the PAATH study

Clinical characteristics[a]	HR participants ($n = 60$)	HVs ($n = 45$)	*p*-value
PANSS, mean (SD) ($n = 6$)			
Positive	13.1 (3.2)	7.1 (0.5)	< 0.001[b]
Negative	12.4 (5.0)	7.8 (0.9)	< 0.001[b]
General psychopathology	32.7 (7.0)	16.3 (1.3)	< 0.001[b]
Sum of all items	58.2 (12.1)	31.3 (1.9)	< 0.001[b]
BDI-II ($n = 11$)			
Sum of all items, mean (SD)	29.9 (12.8)	5.6 (5.5)	< 0.001[b]
Suicidality (score 1–3), *n* (%)	36 (72.0)	4 (9.1)	< 0.001[c]
Depression subgroup, *n* (%)			< 0.001[c]
Minimal (score 0–13)	5 (10.0)	39 (88.6)	< 0.001[c]
Mild (score 14–19)	8 (16.0)	3 (6.8)	0.167[c]
Moderate (score 20–28)	10 (20.0)	2 (4.5)	0.025[c]
Severe (score 29–63)	27 (54.0)	0 (0)	< 0.001[c]
BAI ($n = 15$)			
Sum of all items, mean (SD)	28.2 (11.9)	6.7 (5.6)	< 0.001[b]
Anxiety subgroup, *n* (%)			< 0.001[c]
Minimal (score 0–7)	2 (4.2)	29 (67.4)	< 0.001[c]
Mild (score 8–15)	5 (10.4)	9 (20.9)	0.165[c]
Moderate (score 16–25)	12 (25.0)	5 (11.6)	0.102[c]
Severe (score 26–63)	29 (60.4)	0 (0)	< 0.001[c]
YMRS ($n = 7$)			
Sum of all items, mean (SD)	3.9 (4.1)	0.5 (1.2)	0.001[b]
YBOCS ($n = 13$)			
Having obsession, *n* (%)	37 (77.1)	2 (4.5)	< 0.001[c]
Having compulsion, *n* (%)	34 (70.8)	1 (2.3)	< 0.001[c]
Sum of all items, mean (SD)	20.1 (5.8)	5.3 (1.5)	< 0.001[b]
Severity subgroups, *n* (%)			< 0.001[c]
Subclinical (score 0–7)	2 (5.4)	3 (100)	0.001[d]
Mild (score 8–15)	5 (13.5)	0 (0)	0.001[d]
Moderate (score 16–23)	20 (54.1)	0 (0)	0.231[d]
Severe (score 24–31)	9 (24.3)	0 (0)	1.000[d]
Extreme (score 32–40)	1 (2.7)	0 (0)	1.000[d]

a Number of missing observations in brackets.
b Independent *t*-test.
c Chi-squared test.
d Fisher's exact test.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

TABLE 5 Functioning and quality of life comparison between HR individuals and HVs in the PAATH study

Functioning and quality of life measures[a]	HR participants ($n = 60$)	HVs ($n = 45$)	p-value
GAF, mean (SD) ($n = 3$)			
Symptoms	45.4 (8.9)	86.6 (3.8)	< 0.001[b]
Disability	48.6 (9.4)	86.7 (3.6)	< 0.001[b]
Occupational status, n (%) ($n = 7$)[c]			0.061[d]
Unemployed	20 (37.7)	8 (17.8)	0.029[d]
Employed	16 (30.2)	22 (48.9)	0.058[d]
Student	17 (32.1)	15 (33.3)	0.895[d]
MANSA, mean (SD) ($n = 11$) – satisfied with:	3.8 (1.0)	5.6 (0.6)	< 0.001[e]
Life as a whole today	3.4 (1.5)	5.6 (1.0)	0.001[e]
Health	3.5 (1.4)	5.4 (1.1)	< 0.00[e]
Present mental health	3.0 (1.4)	6.2 (0.8)	< 0.00[e]
Job (if working)	4.1 (1.8)	5.4 (1.4)	0.011[e]
Not working (if not working)	3.7 (1.7)	4.0 (1.9)	0.532[e]
Financial situation	3.5 (1.5)	4.6 (1.5)	0.001[e]
Leisure activities	3.9 (1.9)	5.6 (1.3)	< 0.00[e]
Number of friends	4.2 (1.8)	5.8 (1.0)	< 0.001[e]
Relationships with friends	4.5 (1.7)	5.7 (0.9)	< 0.001[e]
Personal safety	4.0 (1.6)	5.8 (0.9)	< 0.001[e]
Accommodation	4.6 (1.7)	6.0 (1.2)	< 0.001[e]
People one lives with (if living with other)	4.7 (1.4)	6.1 (0.9)	< 0.001[e]
Living alone (if living alone)	4.0 (–)	–	–
Relationship with family	4.0 (1.4)	5.6 (1.0)	< 0.001[e]
Life overall	3.0 (1.4)	5.8 (0.9)	< 0.001[e]

a Number of missing observations in brackets.
b Mann–Whitney *U*-test.
c Employment status is broadly categorised into three groups: 'unemployed' includes subjects who do not have a job – they are looking for work or not looking for work (e.g. housewife) or are not able to work for medical reasons; 'employed' refers to people who have full-/part-time employment or who are employed but are currently unable to work; 'student' refers to full/-part-time students.
d Chi-squared test.
e Independent *t*-test.

Substance use

See *Appendix 10* for the published report of this work.[43]

Research aims

The role of substance use in the development of HR for psychosis or its impact on the transition to full psychotic presentations is overlooked in the literature. The aim of this study was to describe in detail past and current substance use in HR individuals and compare this profile with that of a random sample of HVs recruited from the same geographical area.

Methods for data collection

We recorded information on alcohol and substance use profiles for both groups, including identification of abuse/dependence and influence on psychotic-like experiences. Additionally, differences between HR individuals and HVs were assessed for sex, ethnicity, occupational status, age of lifetime first substance use and prevalence and frequency of substance use.

Analysis

To compare the two groups a two-sample *t*-test was used for age and Fisher's exact test was used for sex, ethnicity and occupational status. Fisher's exact test was also used for assessing the differences between substance use distributions and patterns. The Wilcoxon signed-rank test was employed for non-normally distributed continuous variables (age of lifetime first substance use, frequency of substance use). Box plots were used for graphical representation of the differences in frequency of substance use.

Key findings

High-risk individuals were significantly younger than HVs when they started using alcohol and drugs ($p = 0.014$). This may be important as harmful effects of drugs may differ according to brain development, with younger brains and minds being more vulnerable to deleterious effects. The prevalence of HR substance use was generally similar to that of HV substance use except for past polydrug use, which was higher for HR individuals. HR polydrug users experimented with a wider range of substances than HV polydrug users. Choice of substance was similar when comparing HR individuals' and HVs' current and past use. Alcohol was the most frequently reported substance used in both groups. This was different from previous findings in which cannabis was the most commonly used substance.[44] Cannabis was the most widely used drug in both groups, the use of other illicit substances being considerably lower; the least used substances for both groups were sedatives and opiates.

None of the HR individuals or HVs met the criteria for a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV TR)[45] substance use disorder or dependence. Thus, the HR substance use profile in our sample was significantly different from that of FEP patients in our region at the time of their referral to CAMEO. The pattern of comparatively low use in people with HR mental states could have some influence on psychotic-like experiences but not on transition to a frank psychotic disorder.

The main difference between HR individuals and HVs was the frequency of substance use. Current frequency of use was significantly higher in HR individuals than in HVs for alcohol ($p = 0.001$) and cannabinoids ($p = 0.03$) (*Figure 7*). None of our HR group used cannabis daily. This was contrary to many reports in the literature regarding HR individuals, in which around 60% of participants used these substances.[44] Frequency of substance use for HR individuals was similar for current and past use whereas HVs were more likely to have had a period in the past when they used these substances more frequently (see *Figure 7*). This sustained substance use over a protracted period could be more deleterious than a shorter period of increased use. The higher frequency of substance use in HR individuals combined with a significantly younger age of first use could contribute to the development of psychotic-like experiences.

Limitations

The short follow-up period in this study could explain the low transition rate. In addition, the 3 monthly follow-ups may have been therapeutic and consequently reduced the likelihood of transition. The sociodemographic differences between our groups could also have influenced the findings. HVs were significantly older than HR individuals. In addition, as male sex is associated with substance use in patients and psychotic disorders in the general population, the slightly higher proportion of males in the HR group may have influenced the substance use profiles.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

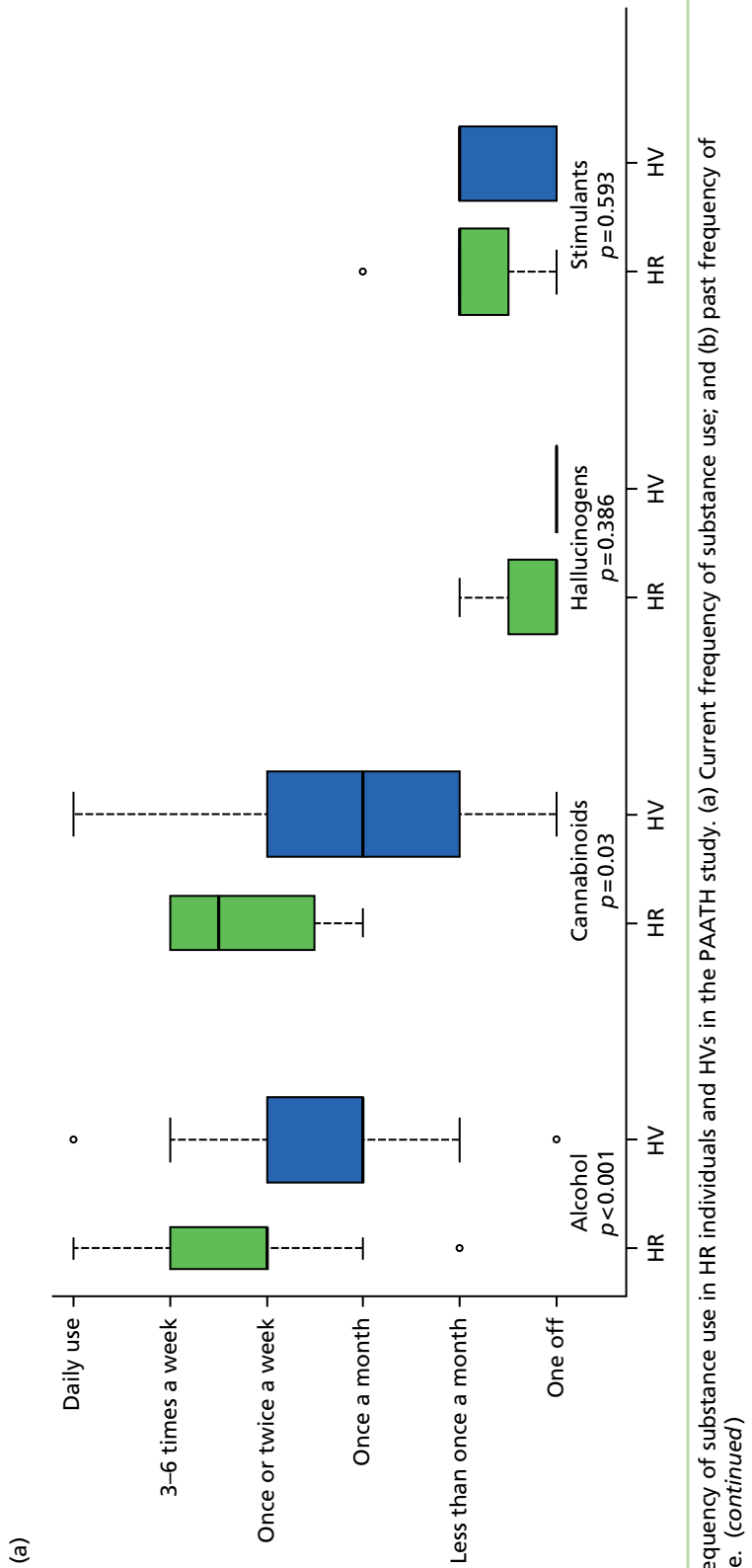


FIGURE 7 Frequency of substance use in HR individuals and HVs in the PAATH study. (a) Current frequency of substance use; and (b) past frequency of substance use. *(continued)*

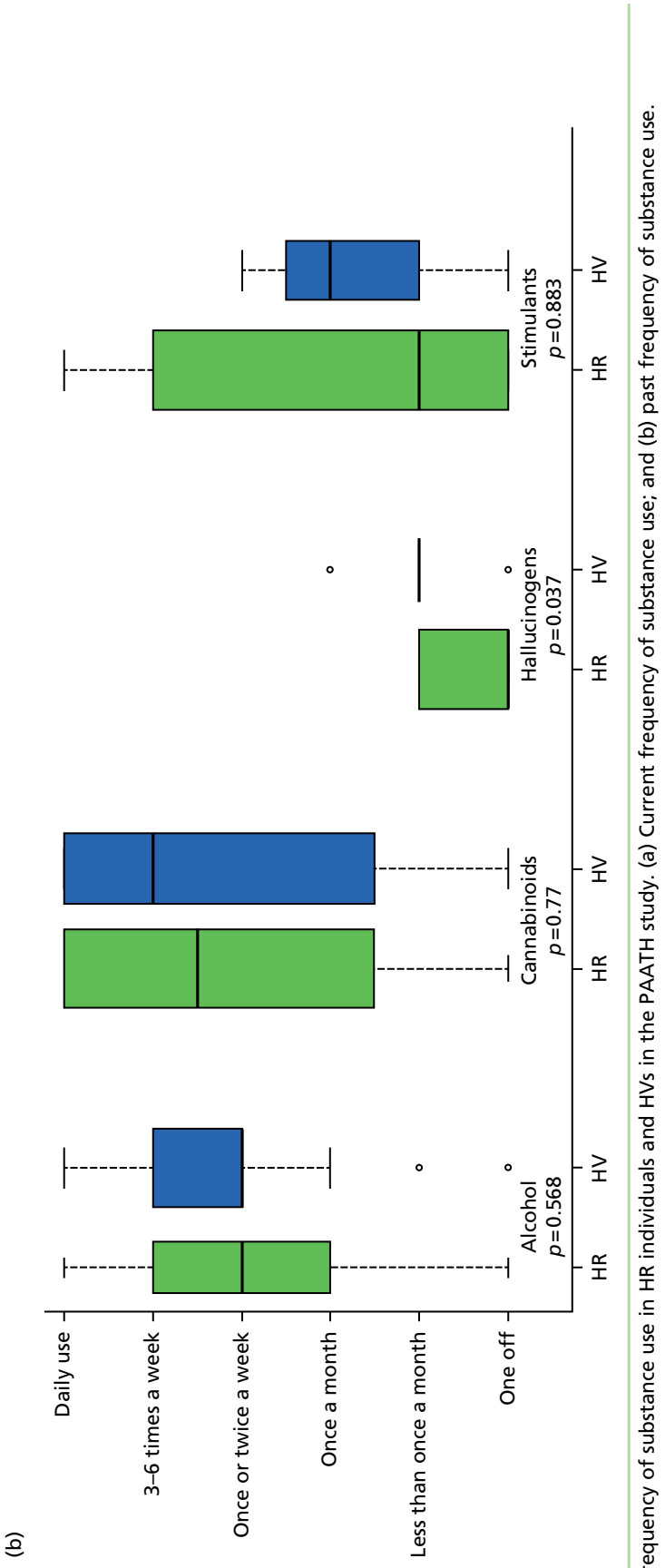


FIGURE 7 Frequency of substance use in HR individuals and HVs in the PAATH study. (a) Current frequency of substance use; and (b) past frequency of substance use.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Recommendations for future research

The pattern of substance use by each individual following their referral to CAMEO was not closely monitored. Future research should include a prospective follow-up to show any changes in patterns of substance use and identify any associations with incidence of psychotic experiences over time.

Substance use in HR individuals requires a greater emphasis and a more detailed consideration in future studies. All of our studies are from secondary analyses in a relatively small sample; the younger age of onset of use in the HR group may be important and, chiming with findings from other studies[44] including birth cohorts, merits further enquiry at clinical and biological levels.

History of psychological, physical and sexual trauma

See *Appendix 11* for the published report of this work.[46]

Research aims

Differences in the experience of trauma such as severity, frequency and age at trauma exposure could result in different responses among individuals and explain the likelihood of developing particular psychiatric symptoms. The aim of this study was to compare the characteristics of the trauma history between young people at HR for psychosis and a sample of HVs recruited from the same geographical area to determine which are more likely to be associated with HR mental states.

Methods for data collection

The Trauma History Screen (THS)[47] was used to enable an assessment of the number and perceived intensity of adverse life events and age at trauma exposure. The BDI-II[36] and BAI[37] were also used to assess the relationship between these factors and depression and anxiety.

Analysis

Fisher's exact test was used to compare demographic information and negative binomial regression was used for the comparison of the total number of traumas and the age at which trauma occurred.

Poisson regression and the *t*-test were used to compare individual traumas and the intensity of trauma respectively. Relationships between age at which trauma occurred, number and intensity of traumas, BDI-II score and BAI score were explored with Pearson correlations. Logistic regression was used to assess the influence of age at trauma exposure and the intensity and number of traumas with regard to the presence of HR mental states. We also presented graphical comparisons of both groups using box plots.

Key findings

High-risk participants had a higher incidence of trauma and reported repeated exposure to trauma compared with HVs. Traumatic events involving physical abuse with intention to harm accounted for the largest proportion of reported trauma for both groups and showed the largest difference between HVs and HR participants. Traumatic events involving sexual abuse were uncommon in both groups.

High-risk participants experienced significantly more traumatic events than HVs ($p \leq 0.001$) but equivalent distress in relation to these events. Although up to 70% of individuals endorsed experiencing distress, in both groups 30–40% of traumatic experiences were not considered to be emotionally distressing. There was only a single case of post-traumatic stress disorder in the whole sample. The perceived intensity of trauma could be a future predictor of psychopathology other than psychosis.

First incidents of trauma and the total number of traumas ($p < 0.001$) occurred at an earlier age for HR participants, who also experienced significantly more traumas during the developmental period between the ages of 0 and 8 years ($p \leq 0.001$) (*Figure 8*). HVs experienced more traumas between the ages of 25 and 35 years and higher instances of trauma occurred between the ages of 9 and 24 years than between

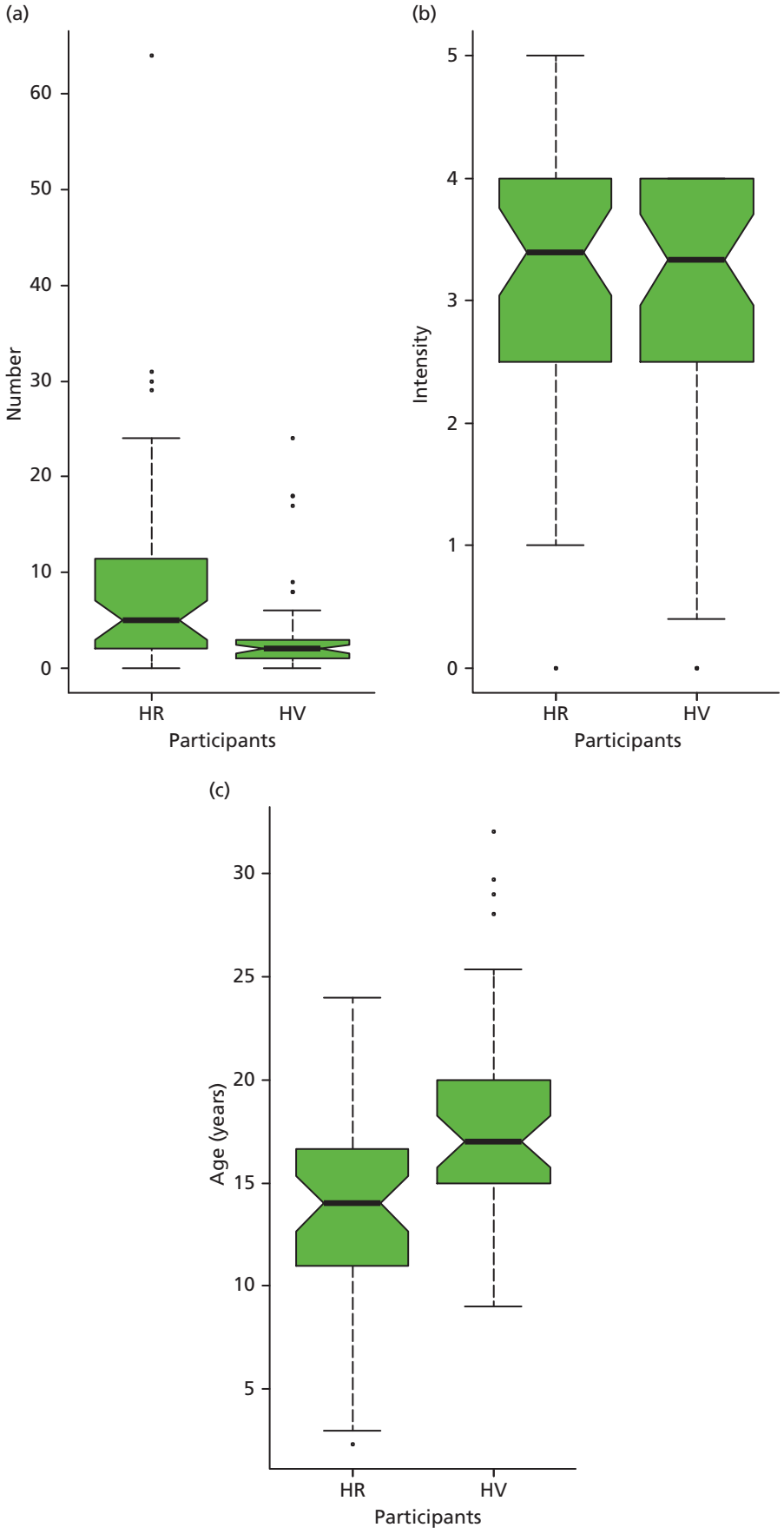


FIGURE 8 Box plots showing (a) the distribution of traumatic events; (b) the intensity of trauma; and (c) the age at trauma exposure for HR and HV participants in the PAATH study.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

the ages of 0 and 8 years. Both incidences of trauma and age at which trauma occurred were the most likely predictors of becoming HR, not the degree of distress reported as a result of the trauma. Higher age for trauma exposure and lack of sexual abuse could be ameliorating factors for the HR individuals in this study.

Higher levels of anxiety ($p \leq 0.001$) and depression ($p \leq 0.001$) were found in our HR group. Combined with the very low transition rates to date, this could be interpreted as a lack of diagnostic specificity and predictive value in the HR model. A HR mental state is not necessarily a specific marker for psychosis. The prevalent co-presence of anxiety and depression in this group indicates that trauma may play a role in this manifestation of symptoms.

Limitations

Trauma was measured only using the respondents' subjective information and not corroborated by independent information. Using a combination of methods would yield the most accurate record of trauma. A valid measure of distress should have been used to elucidate any relationships between distress, trauma, anxiety and psychotic experiences/symptoms.

Although the THS[47] does examine trauma involving physical abuse as a child and events that induce feelings of fear, helplessness and horror, there is no specific question concerning bullying. It is possible that a large proportion of traumatic experiences were missed because of this omission.

Recommendations for future research

We need to understand the emotional impact of trauma on the subjective perceptions of the individual. This can extend our understanding of why particular events cause traumatic stress in particular individuals.

To enable differentiation between psychotic-like experiences that may reflect dissociative responses to trauma and genuine prodromal psychotic presentations, trauma characteristics in individuals at clinical HR should be thoroughly assessed routinely.

First-rank symptoms

See *Appendix 12* for the published report of this work.[48]

Research aims

Kurt Schneider[49] considered certain types of psychotic experience of first-rank importance in deciding whether or not a psychotic syndrome was schizophrenia. These 'first-rank symptoms' (FRSs) remain influential in operational diagnostic criteria today, but there is little work evaluating their significance in HR mental states or even whether or not they occur there at all. Would they predict transition from HR to FEP?

The aims of this study were to describe (1) the prevalence of FRSs among individuals at HR; (2) the association between FRSs and transition to full-blown psychosis; and (3) the level of adjustment of individuals at HR and with FRSs during their childhood (aged 6–11 years) in terms of social and academic functioning. Comparisons were made between a sample of individuals at HR who were referred to an EIS and HVs recruited from the same geographical area.

Methods for data collection

All subjects were assessed by senior research clinicians using the MINI[12] and the PANSS.[35] FRSs were defined according to Kurt Schneider's[49] original classification and information was collected from the PANSS,[35] CAARMS[11] and clinical reports. Early premorbid functioning was measured using the Premorbid Adjustment Scale (PAS).[50] We grouped individuals by number and type of FRSs and analysed transitions to full-blown psychosis over a 2-year follow-up period. We also correlated the general social and functional adjustment of these individuals during their childhood (aged 6–11 years) with the future development of HR mental states and FRSs.

Analysis

Fisher's exact test was used for comparing the categorical sociodemographic variables; for age the *t*-test was used. The Wilcoxon signed-rank test was used to compare PAS domains between HR individuals and HVs. Fisher's exact test was also used to investigate associations between the FRSs in HR individuals and transitions to psychosis.

Key findings

At least one FRS was present in 43.3% of HR individuals and 21.6% of HR individuals had more than one FRS. Auditory hallucinations and passivity experiences were the most commonly reported (*Figure 9*).

Except for passivity experiences, the presence of one or more FRS was not significantly associated with transition to FEP. Compared with HVs, HR individuals, especially those with FRSs, had poorer premorbid functioning and adjustment as children across educational, social and peer relationship domains; however, this was not associated with FEP 2 years later (*Figure 10*).

Strengths

The study was controlled, including both HVs and help-seeking HR individuals. The longitudinal design and high retention rates over 2 years made it possible to address the limitations associated with cross-sectional studies.

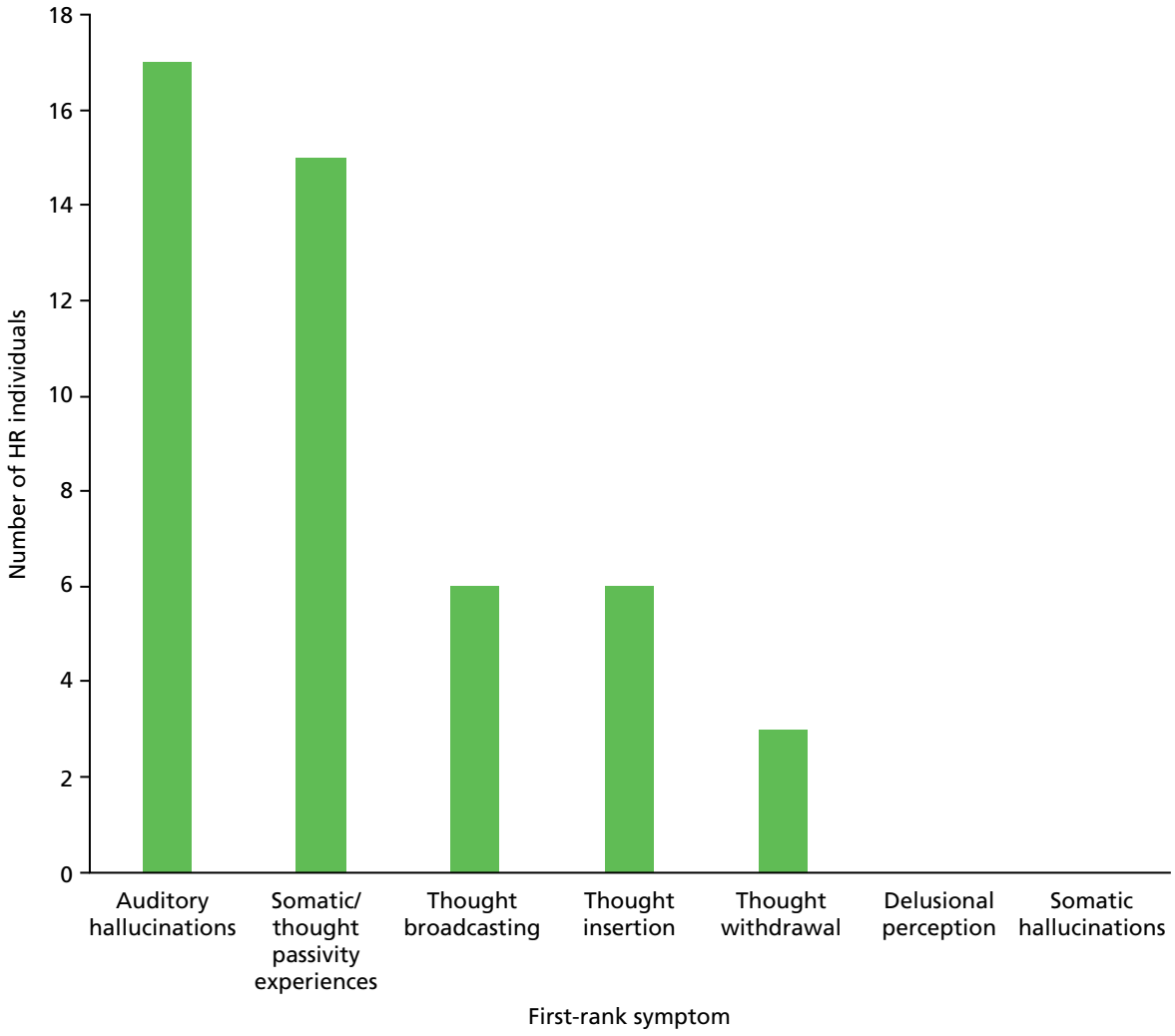


FIGURE 9 Distribution and frequency of FRSs in HR individuals in the PAATH study.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

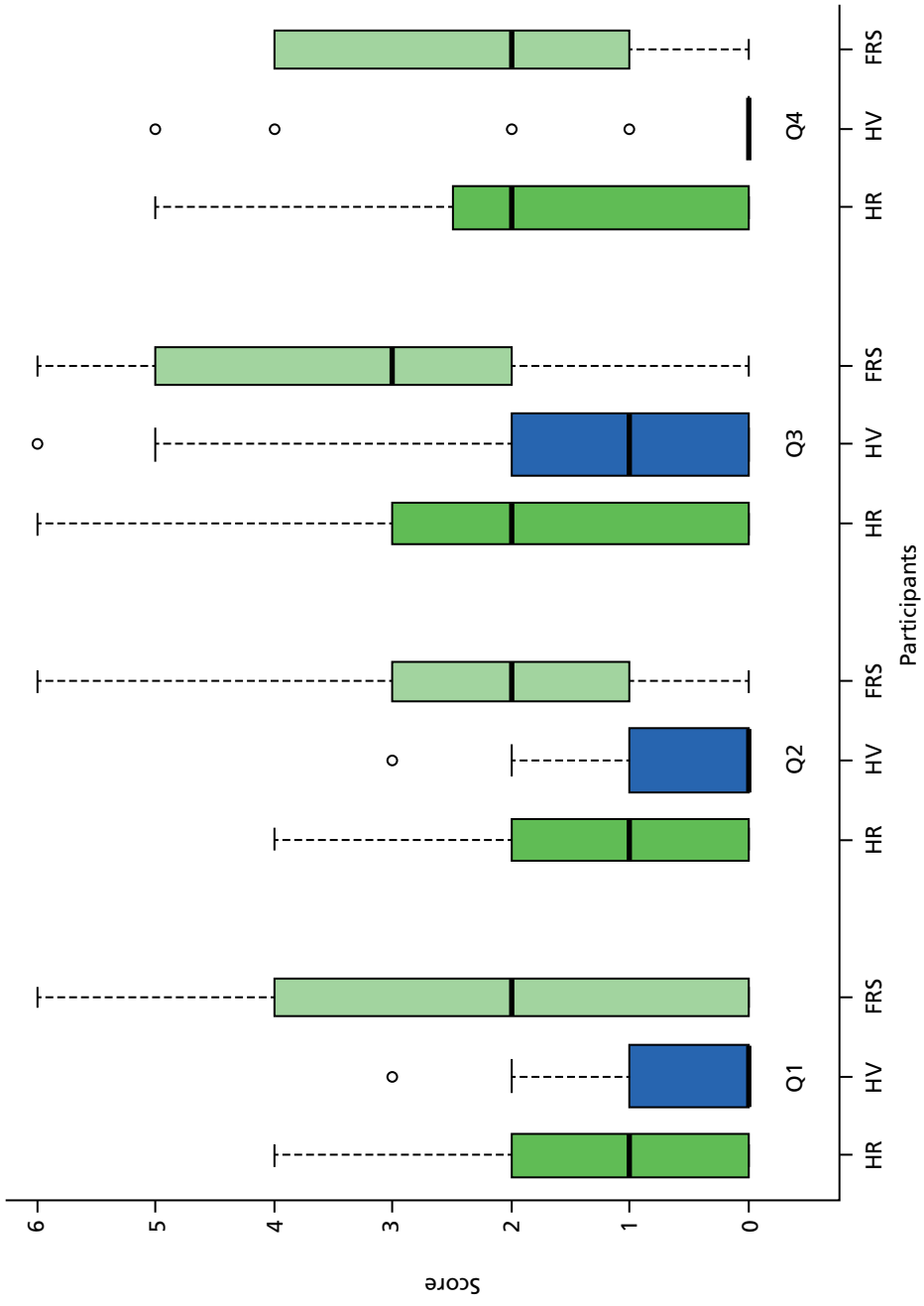


FIGURE 10 Comparison of PAS domains (aged 6–11 years) between HR individuals, HVs and a subgroup of HR individuals with FRSs in the PAATH study. Q1: sociability and withdrawal; Q2: peer relationships; Q3: scholastic performance; Q4: adaptation to school.

Limitations

The sample size did not allow further adjustment for comorbid mental disorders, which may have shed light on specific associations between level of impairment and increased risk for non-psychotic mental disorders.

It was possible that early premorbid adjustment was subject to recall bias because of the retrospective measure employed. In addition, conversion rates to psychosis could have been higher if follow-up had been longer than 2 years.

Studies with larger samples will be required to replicate findings regarding associations between specific FRSs and future conversions to psychosis, especially the relevance of those FRSs that were absent in our sample (somatic hallucinations and delusional perceptions).

Insights from the clinical team

In *Appendix 13* we include a subjective view from the researchers and clinicians who were on the ground delivering the programme and collecting the data. We share this perspective, which could be acquired only through the process of operationalising this programme, reflecting on the merit, worth and significance of our work and providing insights that we hope will guide future research.

Inter-relation between aspects of the programme

It is noteworthy that the elements of our research plan mostly run in parallel, reinforcing each other to successfully achieve most of our aims by the time that this programme ended.

We also significantly enhanced some aspects of the programme through an efficient use of available resources. For example, we systematically followed all individuals at HR for psychosis in the context of a separate, naturalistic, observational design, which is described in *Work package 5*. Furthermore, this study was linked with several epidemiological and neurobiological research projects, representing an example of efficiencies in science.

The Prospective Analysis of At-risk mental states and Transitions into psycHosis study as an example of efficiency in health research

As previously mentioned, the PAATH study enhanced the original grant application through an efficient use of available resources. This study was not only aligned with other epidemiological projects (see *Work package 3*) but also nurtured neurobiological projects, creating a remarkably efficient research network around it that included backwards translation to investigate biological mechanisms underlying the HR state. HR individuals have not often been studied and so this group of 60 research volunteers represented a remarkable resource for other studies. This development was particularly important as the programme grant application did not consider cognitive or neurobiological examinations in the HR sample, which would add valuable information and provide a more comprehensive evaluation of this population cluster. Thus, the NIHR funding had an impact beyond our programme.

Some of these more biological projects that rely on our programme are briefly described in the following sections, including the title, chief investigator and aims. All of these projects were adopted onto the NIHR portfolio.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Neurobiological factors underlying the onset of psychosis

Chief investigators
Professor Philip McGuire and Dr Paul Allen, Institute of Psychiatry, London, UK.

Funder
Wellcome Trust, UK.

Aims
The key objective of this study is to examine the relationship between the medial temporal lobe and glutamatergic, gamma-aminobutyric acid (GABA)ergic and dopaminergic dysfunction in people at HR of psychosis. A further aim is to determine whether or not neuroimaging measures of these factors can be used in a clinical setting to predict the risk of later transition to psychosis in individuals at HR for psychosis.

The influence of cortisol levels on cognitive function and psychotic symptoms in patients with at-risk mental states for psychosis

Chief investigators
Professors Paul Fletcher and Ian Goodyer with Dr Veronika Dobler, University of Cambridge, Cambridge, UK.

Funder
Wellcome Trust, UK.

Aims
The proposed research focuses on particular aspects of the stress–diathesis model by further defining cognitive deficits and exploring the differential impact of variation in circulating cortisol levels (as a biological marker of stress) on current cognitive function in HR. This will be examined in three inter-related studies:

- study 1 – the influence of physiologically induced stress on cognitive function in patients with at-risk mental states for psychosis and age- and sex-matched controls
- study 2 – cognitive and perceptual processing deficits in HR
- study 3 – functional magnetic resonance imaging (fMRI) analysis of brain responses during reward learning processes before and after the induction of stress in HR individuals and age- and sex-matched control subjects.

The learning study

Chief investigator
Dr Graham Murray, University of Cambridge, Cambridge, UK.

Funder
Medical Research Council, UK.

Aims
This study aims to identify brain regions involved in simple learning tasks in patients and HVs using fMRI. Any group differences may inform on both the neurophysiological and the neuropsychological features of mild psychosis. Better insights into these features will be of benefit to patients and their families in making sense of otherwise strange and potentially frightening symptoms and will lead to more informed and appropriate use of currently available treatments and may ultimately lead to novel pharmacological and/or psychological treatments for psychosis.

Summary

This applied health research programme focused on case finding and case ascertainment for psychosis. It was embedded in clinical services with the aim of improving the planning and delivery of those services. Most of our research programme was carried out in our EIS, CAMEO, in the CPFT, in general practices and in sixth-form educational colleges across the county of Cambridgeshire and the city of Peterborough, UK. We also extended some elements of our research to the whole of the East of England. Our overall conclusions from the research are expressed below as implications for practice, set out for each work package, but we begin with some overall comments and reflections on the programme.

To support and facilitate data collection, outcome evaluations and randomised trials in the programme, we successfully developed an IT clinical surveillance system (CAR; see *Work package 1*). We recorded in CAR all HR and FEP cases identified over the course of our programme. This provided a useful blueprint to connect information from patients, services, clinicians and researchers. In fact, our programme consisted of five inter-related work packages that helped us understand the socioepidemiology of psychosis and HR mental states, as well as better identify these clinical presentations in primary care and educational institutions.

The main component of our programme was the LEGS cRCT (see *Work package 4*), in which we educated GPs about HR and FEP and encouraged them to identify and refer young people with these mental states to CAMEO so that they could receive specialist attention or be signposted to other services, if required. Our new theory-based intervention demonstrated that additional expenditure, through the use of tailored intensive liaison between primary and secondary care to identify and help with the referral of individuals with early signs of psychosis, adds clinical and economic value. Such research linking GPs, colleges and mental health services, with input from a NHS trust and university, was challenging but very rewarding. It helped different organisations in the public sector understand each other and, in so doing, helped young people with emerging mental disorders. We are still analysing the results from the educational colleges.

The LEGS cRCT was successfully implemented but we had to manage challenging situations along the way, several of which provide useful lessons. Ethical approval for a cluster trial is a good example. Based on discussions with former REC members, we assumed that only the agreement of practices in the intervention arm would be needed to undertake certain elements of the trial, such as educational sessions. In normal practice it would be up to one organisation to agree with another how they interacted; we had hoped simply to randomise this process. However, in the research context the ethics committee stipulated that formal consent was required from all invited general practices, regardless of which arm of the trial they were assigned to. With > 100 practices to work with and, in many cases, visit, this resulted in a delay in implementing the trial, which required an 18-month no-cost extension that was finally granted by the NIHR. In the future, early liaison with the REC would be recommended at the design phase of the programme.

In addition, the REC considered that the follow-up of young people at HR referred from the LEGS trial, another objective of our programme, had to be carried out as a separate study that required a different REC application and, in consequence, another NHS governance process. Again, careful liaison with the REC at the design stage, before the application was submitted to the NIHR, would have negated this problem.

Nevertheless, clearing what seemed like hurdles at the time ultimately enhanced the programme. For example, the delay in the implementation of the LEGS trial allowed extra time to develop the theory-based educational intervention. A number of practices refused to take part in the research, which reduced our sample size but allowed those general practices that did not consent to make up a PAU comparator, so we retained sufficient statistical power. In addition, by separating the follow-up of individuals at HR from the LEGS trial, we developed a new, naturalistic, observational study, which was not included in our initial application, involving a thorough, systematic follow-up of these young people: the PAATH study (see *Work package 5*).

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

In the PAATH study we followed those identified as being at HR to determine how many would develop a full psychotic illness over 2 years. Interestingly, only 5% of the HR participants made a transition to psychosis, which made it difficult to define or elicit factors associated with conversions (because of very low statistical power). The study was able to contribute to a new understanding of the mental health problems, mainly depression and anxiety, suffered by people at HR, beyond the simple fact that they were experiencing psychotic phenomena. Furthermore, we showed that they had a significant history of psychological trauma during their childhood and adolescence. Indeed, we consider that the PAATH study contributed to the growing evidence suggesting relationships between depression, anxiety and psychotic experiences in young people without psychotic disorders. The HR mental state is not necessarily simply a harbinger of psychotic illness but a marker of previous psychological trauma, depression and anxiety in people with marked functional impairment.

When we studied the geographical distribution of HR individuals in comparison with that of HVs and those with FEP across Eastern England, the pattern of elevated risk at the neighbourhood level was similar for both HR and FEP participants relative to HVs, suggesting either that social drift, when it happened, began in the prodromal phase or that the exposure of young people to higher socioeconomic deprivation increased the risk of psychosis. This finding formed part of a wider work package (see *Work package 3*) in which we looked into the incidence of psychosis across Eastern England and social and epidemiological factors associated with variations in incidence rates. A series of epidemiological studies, including the SEPEA study in the Eastern region, helped us develop a prediction tool for the incidence of psychotic disorders in England and Wales, made freely available online (see www.PsyMaptic.org) to provide health-care commissioners with accurate forecasts of FEP incidence based on robust epidemiology and anticipated local population need.

We successfully completed most components of our programme but we did not develop a tool to understand predictors of and barriers to recovery in FEP as we had initially planned. This aspect of the programme was deemed to be redundant because of the adoption of the HoNOS by our host NHS trust and throughout the NHS, particularly the version amended to support funding of services according to their activity and outcomes (PbR). At the time this appeared to undermine the importance and viability of this element of our programme but, as we have noted elsewhere, PbR for mental health services is not yet implemented at the time of writing this report and the research may indeed have been useful.

Recommendations for future research

We have set out a series of specific recommendations for future research in each of our work packages. Our general recommendation refers to the particular challenges and unsuccessful elements of the programme, intimately linked with the complex and evolving nature of the NHS. In retrospect, we would have benefited from a Programme Steering Group as is now required by the NIHR. Better intelligence regarding the agenda for changes in the NHS would have helped to mitigate if not avoid some of the challenges that we encountered. In our opinion, the Programme Steering Group membership should include not only academic advisors but also trust board-level executive members, ensuring direct dialogue so that the research programme is fully embedded in the NHS host's business agenda.

Implications for practice

The outputs produced by this programme are already having a significant impact on clinical practice and commissioning in the NHS.

PsyMaptic, our prediction tool for the incidence of psychotic disorders in England and Wales, appeared in the *Annual Report of the Chief Medical Officer 2013* and is already being used for service planning in the UK. Also, the findings from the LEGS cRCT, whose methodology and economic modelling were praised by the author of a commentary on our work in *The Lancet*,[13] have recently been included in the commissioning guidelines[9] for early intervention in psychosis in the UK. Both PsyMaptic and the LEGS cRCT are in line with the 2014 announcement from the UK government of patient waiting time targets being extended to mental health in general and HR and FEP patients in particular.[51] Furthermore, we significantly added evidence to a new understanding of the HR mental state in young people. Only one in 20 participants in the PAATH study moved into a psychotic illness. This is far fewer than initially anticipated but is in line with, and forms part of, a recently accumulating body of evidence. Furthermore, the majority of the entire HR group suffered from depression and anxiety meriting clinical attention and impinging on their daily function. Many of this group had experienced significant psychological or physical abuse, which requires careful exploration and resolution given that these traumatic events may play a central role in the causation of the mental distress. Thus, such people with psychotic experiences but without a psychotic illness should receive timely, appropriate and effective help for their current mental health problems, ideally in a non-stigmatising clinical setting such as primary care, rather than just monitoring to see whether or not they develop a full psychotic illness. This view inspired a new application to the NIHR for a successor programme.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Acknowledgements

The authors thank staff, users and families within CPFT's CAMEO services for their help and support in the prosecution of this research programme as well as those who contributed to the production of this report.

Contributions of authors

Jesus Perez was the principal investigator, **Michelle Painter** was the project manager and **Peter B Jones** was the chief investigator for this programme. **Tim Croudace** and **Peter B Jones** designed the programme. **James B Kirkbride** led the analysis, data extrapolation and interpretation of the epidemiological studies. He also led the development of the PsyMaptic tool. **Debra A Russo** elaborated the theoretical basis of the LEGS intervention and collected the data for the pilots in educational institutions and primary care. All authors contributed to the development of educational materials within the LEGS trial. **Jan Stochl** and **Tim J Croudace** conducted the sample size calculations, statistical analysis and random assignment of participants. **Gillian F Shelley** and **Carolyn M Crane** implemented the LEGS interventions and conducted the PAATH assessments. **Gillian F Shelley** and **Carolyn M Crane** also contributed insights from the clinical team. **Jesus Perez**, **Debra A Russo** and **Peter B Jones** drafted the report. All authors provided a critical review and final approval of the report.

Data sharing statement

All available data can be obtained from the corresponding author.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

References

1. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, *et al.* Randomized controlled trial of the effect on quality of life of second- vs. first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 2006;**63**:1079–87. http://dx.doi.org/10.1001/archpsyc.63.10.1079
2. Department of Health. *The NHS Plan: A Plan for Investment, a Plan for Reform*. London: Department of Health; 2000.
3. Barnett JH, McDougall F, Xu MK, Croudace TJ, Richards M, Jones PB. Childhood cognitive function and adult psychopathology: associations with psychotic and non-psychotic symptoms in the general population. *Br J Psychiatry* 2012;**201**:124–30. http://dx.doi.org/10.1192/bjp.bp.111.102053
4. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2005;**62**:975–83. http://dx.doi.org/10.1001/archpsyc.62.9.975
5. Department of Health. *The Mental Health Policy Implementation Guideline*. London: Department of Health; 2001.
6. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, *et al.* Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center ÆSOP study. *Arch Gen Psychiatry* 2006;**63**:250–8. http://dx.doi.org/10.1001/archpsyc.63.3.250
7. Morrison AP, French P, Stewart SL, Fowler D, Gumley AI, Birchwood M, *et al.* Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *BMJ* 2012;**344**:e2233. http://dx.doi.org/10.1136/bmj.e2233
8. Kelleher I, Keeley H, Corcoran P, Wigman JT, Devlin N, Ramsay H, *et al.* Clinico-pathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *Br J Psychiatry* 2012;**201**:26–32. http://dx.doi.org/10.1192/bjp.bp.111.101543
9. NHS England. *Guidance on New Mental Health Standards Published*. 13 February 2015. URL: www.england.nhs.uk/2015/02/mh-standards/ (accessed 22 January 2016).
10. Preti A, Pisano A, Cascio MT, Galvan F, Monzani E, Meneghelli A, *et al.* Validation of the Health of the Nation Outcome Scales as a routine measure of outcome in early intervention programmes. *Early Interv Psychiatry* 2012;**6**:423–31. http://dx.doi.org/10.1111/j.1751-7893.2011.00329.x
11. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, *et al.* Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry* 2005;**39**:964–71. http://dx.doi.org/10.1080/j.1440-1614.2005.01714.x
12. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59**(Suppl. 20):22–33.
13. Kearns B. Improved identification of people at risk of psychosis: is it value for money? 19 August 2015. URL: www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366(15)00175-3.pdf (accessed 22 January 2016).
14. Angus D. Fusing randomized trials with big data: the key to self-learning health care systems? *JAMA* 2015;**314**:767–8. http://dx.doi.org/10.1001/jama.2015.7762
15. Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991;**50**:179–211. http://dx.doi.org/10.1016/0749-5978(91)90020-T

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

16. Medical Research Council. *Developing and Evaluating Complex Interventions: New Guidance*. 2008. URL: www.mrc.ac.uk/documents/pdf/complex-interventions-guidance/ (accessed 23 January 2016).

17. Critchlow HM, Herrington P, Gunton S. Inside an unquiet mind. Music and science join forces to explore mental ill health. *EMBO Rep* 2012;**13**:95–9. http://dx.doi.org/10.1038/embor.2011.255

18. Coid JW, Kirkbride JB, Barker D, Cowden F, Stamps R, Yang M, *et al.* Raised incidence rates of all psychoses among migrant groups: findings from the East London first episode psychosis study. *Arch Gen Psychiatry* 2008;**65**:1250–8. http://dx.doi.org/10.1001/archpsyc.65.11.1250

19. Health and Social Care Information Centre. *Mental Health and Learning Disabilities Data Set*. 2013. URL: www.hscic.gov.uk/mhldds (accessed 19 January 2016).

20. Cheng F, Kirkbride JB, Lennox BR, Perez J, Masson K, Lawrence K, *et al.* Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting. *Psychol Med* 2011;**41**:949–58. http://dx.doi.org/10.1017/S0033291710002461

21. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization; 1992.

22. Kirkbride JB, Stubbins C, Jones PB. Psychosis incidence through the prism of early intervention services. *Br J Psychiatry* 2012;**200**:156–7. http://dx.doi.org/10.1192/bjp.bp.111.094896

23. Rucker J, Newman S, Gray J, Gunasinghe C, Broadbent M, Brittain P, *et al.* OPCRIT+: an electronic system for psychiatric diagnosis and data collection in clinical and research settings. *Br J Psychiatry* 2011;**199**:151–5. http://dx.doi.org/10.1192/bjp.bp.110.082925

24. Kirkbride JB, Jackson D, Perez J, Fowler D, Winton F, Coid JW, *et al.* A population-level prediction tool for the incidence of first-episode psychosis: translational epidemiology based on cross-sectional data. *BMJ Open* 2013;**3**:e001998. http://dx.doi.org/10.1136/bmjopen-2012-001998

25. Kirkbride JB, Stochl J, Zimbrón J, Crane CM, Metastasio A, Aguilar E, *et al.* Social and spatial heterogeneity in psychosis proneness in a multilevel case–prodrome–control study. *Acta Psychiatr Scand* 2014;**132**:283–92. http://dx.doi.org/10.1111/acps.12384

26. Department for Communities and Local Government. *English Indices of Deprivation 2010*. 2010. URL: http://data.gov.uk/dataset/index-of-multiple-deprivation/ (accessed 22 January 2016).

27. Russo DA, Stochl J, Croudace TJ, Graffy JP, Youens J, Jones PB, *et al.* Use of the theory of planned behaviour to assess factors influencing the identification of individuals at ultra-high risk for psychosis in primary care. *Early Interv Psychiatry* 2012;**6**:265–75. http://dx.doi.org/10.1111/j.1751-7893.2011.00296.x

28. Francis JJ, Eccles MP, Johnston M, Whitty P, Kaner E, Smith L, *et al. Constructing Questionnaires Based on the Theory of Planned Behaviour. A Manual for Health Services Researchers*. Newcastle upon Tyne: Centre for Health Services Research, Newcastle University; 2004. URL: http://openaccess.city.ac.uk/id/eprint/1735 (accessed 19 January 2016).

29. Samejima F. Estimation of latent ability using a response pattern of graded scores. *Psychometrika Monogr Suppl* 1969;**34**:100–14.

30. Perez J, Russo DA, Stochl J, Byford S, Zimbron J, Graffy JP, *et al.* Comparison of high and low intensity contact between secondary and primary care to detect people at ultra-high risk for psychosis: study protocol for a theory-based, cluster randomized controlled trial. *Trials* 2013;**14**:222. http://dx.doi.org/10.1186/1745-6215-14-222

31. Perez J, Jin H, Russo DA, Stochl J, Painter M, Shelley G, *et al.* Clinical effectiveness and cost-effectiveness of tailored, intensive liaison between primary and secondary care to detect individuals at risk of a first psychotic illness (the LEGS study): a cluster-randomised controlled trial. *Lancet Psychiatry* 2015;**2**:984–93. http://dx.doi.org/10.1016/S2215-0366(15)00157-1

32. Russo DA, Stochl J, Painter, M, Shelley GF, Jones PB, Perez J, *et al.* Use of the theory of planned behaviour to assess factors influencing the identification of students at clinical high-risk for psychosis in 16+ education. *BMC Health Serv Res* 2015;**15**:411. http://dx.doi.org/10.1186/s12913-015-1074-y

33. National Institute for Health and Care Excellence. *Psychosis and Schizophrenia in Adults: Prevention and Management*. NICE guidelines CG178. London: NICE; 2014. URL: www.nice.org.uk/guidance/cg178 (accessed 22 January 2016).

34. Hui C, Morcillo C, Russo DA, Stochl J, Shelley GF, Painter M, *et al.* Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. *Schizophr Res* 2013;**148**:175–80. http://dx.doi.org/10.1016/j.schres.2013.05.026

35. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1986;**13**:261–76. http://dx.doi.org/10.1093/schbul/13.2.261

36. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *J Pers Assess* 1996;**67**:588–97. http://dx.doi.org/10.1207/s15327752jpa6703_13

37. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1998;**56**:893–7. http://dx.doi.org/10.1037/0022-006X.56.6.893

38. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensibility. *Br J Psychiatry* 1978;**133**:429–35. http://dx.doi.org/10.1192/bjp.133.5.429

39. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, *et al.* The Yale–Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989;**46**:1006–11. http://dx.doi.org/10.1001/archpsyc.1989.01810110048007

40. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;**33**:766–71. http://dx.doi.org/10.1001/archpsyc.1976.01770060086012

41. Priebe S, Huxley P, Knight S, Evans S. Application and results of the Manchester Short Assessment of Quality of Life (MANSA). *J Soc Psychiatry* 1999;**45**:7–12. http://dx.doi.org/10.1177/002076409904500102

42. Stochl J, Khandaker GM, Lewis G, Perez J, Goodyer IM, Zammit S, *et al.* Mood, anxiety and psychotic phenomena measure a common psychopathological factor. *Psychol Med* 2015;**45**:1483–93. http://dx.doi.org/10.1017/S003329171400261X

43. Russo DA, Stochl J, Painter M, Jones PB, Perez J. Substance use in people at clinical high-risk for psychosis. *BMC Psychiatry* 2014;**14**:361. http://dx.doi.org/10.1186/s12888-014-0361-1

44. Addington J, Case N, Saleem MM, Auther AM, Cornblatt BA, Cadenhead KS. Substance use in clinical high risk for psychosis: a review of the literature. *Early Interv Psychiatry* 2014;**8**:104–12. http://dx.doi.org/10.1111/eip.12100

45. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, text revision. Washington, DC: American Psychiatric Association; 2000.

46. Russo DA, Stochl J, Painter M, Dobler V, Jackson E, Jones PB, *et al.* Trauma history characteristics associated with mental states at clinical high risk for psychosis. *Psychiatry Res* 2014;**220**:237–44. http://dx.doi.org/10.1016/j.psychres.2014.08.028

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

47. Carlson EB, Smith SR, Palmieri PA, Dalenberg C, Ruzek JI, Kimerling R, *et al.* Development and validation of a brief self-report measure of trauma exposure: the Trauma History Screen. *Psychol Assess* 2011;**23**:463–77. http://dx.doi.org/10.1037/a0022294

48. Morcillo C, Stochl J, Russo DA, Zambrana A, Ratnayake N, Jones PB, *et al.* First-rank symptoms and premorbid adjustment in young individuals at increased risk of developing psychosis. *Psychopathology* 2015;**48**:120–6. http://dx.doi.org/10.1159/000369859

49. Schneider K. *Clinical Psychopathology*. New York, NY: Grune & Stratton; 1959.

50. Larsen TK, Friis S, Haahr U, Johannessen JO, Johannessen JO, Melle I, *et al.* Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *Br J Psychiatry* 2004;**185**:108–15. http://dx.doi.org/10.1192/bjp.185.2.108

51. Department of Health. *Mental Health Services: Achieving Better Access by 2020*. London: Department of Health; 2014. URL: www.gov.uk/government/publications/mental-health-services-achieving-better-access-by-2020 (accessed 21 January 2016).

Appendix 1 Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting

Psychological Medicine (2011), **41**, 949–958. © Cambridge University Press 2010
doi:10.1017/S0033291710002461

ORIGINAL ARTICLE

Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting

F. Cheng[1,2,3], J. B. Kirkbride[1,2], B. R. Lennox[1,2], J. Perez[3], K. Masson[3], K. Lawrence[3], K. Hill[4], L. Feeley[3], M. Painter[2], G. K. Murray[1,2,3], O. Gallagher[3,5], E. T. Bullmore[1,2] and P. B. Jones[1,2]*

[1] *University Department of Psychiatry, University of Cambridge, UK*
[2] *NIHR CLAHRC for Cambridgeshire and Peterborough, Douglas House, Cambridge, UK*
[3] *CAMEO, Block 14, Ida Darwin, Fulbourn, Cambridge, UK*
[4] *Norfolk and Waveney Mental Health NHS Foundation Trust, Hellesdon Hospital, Norwich, UK*
[5] *NHS Greater Glasgow and Clyde, UK*

Background. Early Intervention in Psychosis Services (EIS) for young people in England experiencing first-episode psychosis (FEP) were commissioned in 2002, based on an expected incidence of 15 cases per 100 000 person-years, as reported by schizophrenia epidemiology in highly urban settings. Unconfirmed reports from EIS thereafter have suggested higher than anticipated rates. The aim of this study was to compare the observed with the expected incidence and delineate the clinical epidemiology of FEP using epidemiologically complete data from the CAMEO EIS, over a 6-year period in Cambridgeshire, for a mixed rural–urban population.

Method. A population-based study of FEP (ICD-10, F10–39) in people aged 17–35 years referred between 2002 and 2007; the denominator was estimated from mid-year census statistics. Sociodemographic variation was explored by Poisson regression. Crude and directly standardized rates (for age, sex and ethnicity) were compared with pre-EIS rates from two major epidemiological FEP studies conducted in urban English settings.

Results. A total of 285 cases met FEP diagnoses in CAMEO, yielding a crude incidence of 50 per 100 000 person-years [95% confidence interval (CI) 44.5–56.2]. Age- and sex-adjusted rates were raised for people from black ethnic groups compared with the white British [incidence rate ratio (IRR) 2.1, 95% CI 1.1–3.8]. Rates in our EIS were comparable with pre-EIS rates observed in more urban areas after age, sex and ethnicity standardization.

Conclusions. Our findings suggest that the incidence observed in EIS is far higher than originally anticipated and is comparable to rates observed in more urban settings prior to the advent of EIS. Sociodemographic variation due to ethnicity and other factors extend beyond urban populations. Our results have implications for psychosis aetiology and service planning.

Received 17 February 2010; Revised 9 November 2010; Accepted 13 November 2010; First published online 23 December 2010

Key words: Early intervention in psychosis, epidemiology, health services research, incidence, psychotic disorders, public health.

Introduction

Much of our knowledge about the clinical epidemiology of psychotic disorders comes from studies based in predominately urban settings, often cities (March *et al*. 2008), and predicated on health service models that have evolved considerably since the evidence was gathered. These studies have indicated a rich landscape of variation in incidence according to standard epidemiological dimensions such as age, sex, social class and ethnicity (McGrath *et al*. 2004), with further, compound effects visible at the urban neighbourhood level including ethnic density (Kirkbride *et al*. 2008*a*). Far less is known about psychosis epidemiology and its public health impact across the full gamut of population settlements, including mixed urban, suburban and rural populations in which the majority of the population lives, a gap that has implications for our

* Address for correspondence: Professor P. B. Jones, University Department of Psychiatry, University of Cambridge, Herchel Smith Building for Brain and Mind Sciences, Forvie Site, Cambridge Biomedical Campus, Cambridge CB2 0SX, UK.
(Email: pbj21@cam.ac.uk)

The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <http://creativecommons.org/licenses/by-nc-sa/2.5/>. The written permission of Cambridge University Press must be obtained for commercial re-use.

© Cambridge University Press 2010. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <http://creativecommons.org/licenses/by-nc-sa/2.5/>. The written permission of Cambridge University Press must be obtained for commercial re-use.

understanding of causation and for health service provision based on population need.

Nevertheless, major changes have been made to publicly funded mental health services for young adults with first-episode psychotic disorders in the UK, Australia and several European countries. In England, Early Intervention in Psychosis Services (EIS) were introduced in 2002 for young people, aged 14–35 years, presenting to services with symptoms of psychosis who receive a tailored package of care for 3 years before discharge or transfer to appropriate services. Staffing levels were specified on the basis of anticipated incidence rates in the region of 12 to 15 per 100 000 person-years (Department of Health, 2001; Lester *et al*. 2009). The logic for the EI approach included the association between longer duration of untreated psychosis and poorer functional outcome (Marshall *et al*. 2005), and some evidence from randomized designs that EIS may improve the outcome for young people with psychosis, in terms of fewer relapses, readmissions, symptoms (Craig *et al*. 2004; Grawe *et al*. 2006) and cost-effectiveness (Mihalopoulos *et al*. 2009). However, a Cochrane review on the benefits of EIS concluded that there was insufficient evidence from randomized control trials to draw definitive conclusions as to their effectiveness (Marshall & Rathbone, 2008). A further follow-up study suggested that any gains were not sustained at 5 years (Bertelsen *et al*. 2008). A decade since their introduction in England, EIS remain controversial (Marshall & Rathbone, 2008; Bosanac *et al*. 2010; Kuehn, 2010; McGorry *et al*. 2010; Pelosi & Birchwood, 2003) but are the front line for young people who develop psychotic illness.

There have been anecdotal reports of higher than expected caseloads in some, but not all, English EIS. If borne out by epidemiological data, there may be service-based reasons for this, such as the systematic inclusion of 'false-positive' cases boosting caseloads, in addition to the possibility that the original epidemiological predictions (Department of Health, 2001) may have been inadequate, particularly when rates from urban areas were applied indiscriminately to rural settings. These explanations are not mutually exclusive, and can be interrogated using high-quality epidemiological data.

We took the opportunity to estimate the administrative incidence of psychosis and its variation along sociodemographic dimensions using as a case ascertainment system developed in a well-established EIS, CAMEO (www.cameo.nhs.uk), which serves South Cambridgeshire, a mixed urban–rural area of eastern England. Building on our previous epidemiological studies of clinically relevant psychosis, such as the East London First Episode Psychosis (ELFEP) study (Coid *et al*. 2008) and the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study (Kirkbride *et al*. 2006), we designed this EIS on the same epidemiological principles that were used in these studies and the progenitor studies organized by the World Health Organization (WHO; Jablensky & Sartorius, 2008), so as to facilitate clinical research in a population-based service (Barnett *et al*. 2007). Similarly, the clinical inclusion criteria were based on clinically relevant psychotic illness rather than the so-called at-risk mental states (ARMS), people with the latter conditions being excluded from the service.

Using data from a 6-year period (2002–2007) we aimed to estimate: (1) the incidence of clinically relevant psychosis in a mixed urban and rural catchment area of the EIS; (2) whether incidence rates were comparable to rates in urban English settings generated by the AESOP and ELFEP studies (conducted prior to the introduction of EIS); and (3) whether rates varied by age, sex and ethnicity as in the urban studies. We hypothesized that age-adjusted rates would be lower than those found in more urban areas of the UK (Kirkbride *et al*. 2006; Coid *et al*. 2008) because there is consistent evidence that incidence rates of psychotic disorders are higher in increasingly urban environments (McGrath *et al*. 2004; March *et al*. 2008).

Setting

South Cambridgeshire had an estimated population of 505 978 people in 2007 (ONS, 2009*a*), of whom over 30% ($n = 156\,058$) fell within the age range of 17–35 years covered by the CAMEO service. It includes rural areas, small market towns and the university city of Cambridge, where 36% of the eligible population reside. In terms of ethnicity, the population at risk is predominantly white British (an estimated 76% in 2007), but with substantial proportions of non-British white (9.7%), Indian (2.6%), Chinese (2.5%) and black African (1.4%) groups. For various reasons, including European Union (EU) expansion in 2004 to include several Eastern European countries, the proportion of the population at-risk from minority ethnic groups has increased from an estimated 20% in 2002 to 24% in 2007. The region is relatively affluent compared with other parts of England; approximately 86% of our population at-risk (aged 17–35) lived in neighbourhoods less deprived than the median for England in 2007 (Noble *et al*. 2008). However, substantial pockets of local deprivation exist in the north of the region, including northern parts of Cambridge city and the rural Fenlands.

Method

Study design

We collected data on all people presenting to CAMEO with a potential first episode of psychotic disorder. CAMEO is a National Health Service (NHS)-funded service that offers management for people aged 17–35 years suffering from FEP in Cambridgeshire. The service was commissioned in clearly defined stages, progressively expanding the catchment area in the following way: CAMEO started on 1 January 2002 in Cambridge, South Cambridgeshire, Royston and East Cambridgeshire. The latter two areas left the service on 30 November 2004 due to funding problems but rejoined on 1 June 2007, at which point the service area was also expanded to Huntingdonshire, a district of Cambridgeshire. For the purposes of this study, the cut-off date for inclusion of subjects was 31 December 2007. Data from Peterborough and North Cambridgeshire were not included in the present investigation because the service has been established only recently.

Referrals to the CAMEO service were received from multiple sources including general practitioners (GPs), psychiatric services (secondary care), school and college counsellors, relatives and self-referrals. Efforts were made to promote the service (by raising awareness of psychosis and promoting prompt referral for assessment of suspected cases) throughout the region through ongoing advertising within mental health services and educational lectures, visits to and liaison with GP surgeries, schools and colleges, posting leaflets to all GPs and making introductions during induction courses for mental health staff.

Case ascertainment

All subjects aged 17–35 years presenting to the CAMEO service with a first episode of psychosis, as defined by the Melbourne criteria of the presence of psychotic symptoms for at least 1 week (McGorry *et al*. 1996) and duration of antipsychotic treatment of under 6 months at the time of initial assessment, were screened. Referrals were assessed weekly by specialist clinicians, using the semi-structured Positive and Negative Syndrome Scale (PANSS) interview (Kay *et al*. 1987). All assessments were then discussed with the multidisciplinary team (including at least one or all of the following authors: B.R.L., J.P., G.K.M., E.T.B. or P.B.J.) to ensure that referrals met intake criteria for an ICD-10 psychotic disorder (F10–39), including schizophrenia, bipolar disorders, psychotic depression, schizo-affective disorder, delusional disorder, schizophreniform disorder, substance induced disorders or psychosis not otherwise specified (NOS). Substance misuse was an exclusion criterion only where psychotic phenomena were clearly and solely present in the context of intoxication. Subjects meeting the inclusion criteria were accepted into the clinical service and so counted in the numerator for the present study. Information on ethnicity was obtained by self-ascription using standard categories. Other demographic data, such as age-at-contact and sex were obtained from subjects during initial assessments.

Population at-risk

We estimated the denominator population, aged 17–35, in our study areas by using annual mid-term census estimates provided by the Office for National Statistics (ONS) between 2002 and 2007. Mid-year census estimates, stratified by age (yearly), sex and ethnicity, were calculated using annual birth and death rates among different ethnic groups in the UK projected onto the previous year's estimates (or the 2001 Census itself for 2002 estimates) with adjustment made for immigration and emigration (ONS, 2009*a*). These estimates were not published below local authority level, meaning we had to estimate the yearly population at-risk in one subdistrict of our catchment area (Royston; $n = 3629$) from the 2001 Census. The estimated denominator data were adjusted to take into account changes in the CAMEO catchment area during the study period.

Statistical analyses

Variable coding

We considered all clinically relevant psychotic disorders (F10–39) as the variable defining the numerator that, together with denominator data, was stratified by age (17–19, 20–24, 25–29, 30–35 years), sex, ethnicity and calendar year of inclusion. Because of the low number of minority ethnic groups in our sample, we used four broad ethnicity groupings: white British, non-British white groups, black ethnicities (Caribbean, African and other black groups), and all other ethnicities. We included calendar year as an independent variable to assess and adjust for any changes in incidence (or effectiveness of case finding) over the study period.

To interpret whether incidence rates in our sample were higher than would be expected, we compared our rates with those upon which EIS were predicated (Department of Health, 2001), and also with incidence rates from the two recent observational studies of FEP, mentioned earlier. These covered four urban catchment areas of the UK: East London (the ELFEP study; Coid *et al*. 2008) and Southeast London, Nottingham

© Cambridge University Press 2010. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <http://creativecommons.org/licenses/by-nc-sa/2.5/>. The written permission of Cambridge University Press must be obtained for commercial re-use.

Table 1. *Basic demographic characteristics of sample and crude incidence rates in the CAMEO study*

Denominator population	Cases *n* (%)	Population at-risk *n* (%)	χ^2 test χ^2 (df), *p* value	Crude incidence rate (95% CI)
Total	285 (100.0)	569 921 (100.0)		50.0 (44.5–56.2)
Men	196 (68.8)	296 033 (51.9)	32.3 (1), <0.001	66.2 (57.6–76.2)
Women	89 (31.2)	273 888 (48.1)		32.5 (26.4–40.0)
Age group (years)				
17–19	78 (27.4)	87 962 (15.4)	58.0 (3), <0.001	88.7 (71.0–110.7)
20–24	110 (38.6)	170 825 (30.0)		64.4 (53.4–77.6)
25–29	54 (18.9)	141 182 (24.8)		38.2 (29.3–49.9)
30–35	43 (15.1)	169 952 (29.8)		25.3 (18.8–34.1)
Ethnicity				
White British	206 (72.3)	438 100 (76.9)	5.7 (3), 0.13	47.0 (41.0–53.9)
Non-British white	28 (9.8)	56 655 (9.9)		49.4 (32.8–71.4)
Black	11 (3.9)	11 682 (2.0)		94.2 (47.0–168.5)
Other	27 (9.5)	63 484 (11.1)		42.5 (28.0–61.9)
Unknown	13 (4.6)	–	–	–

df, Degrees of freedom; CI, confidence interval.

and Bristol (the AESOP study; Kirkbride *et al*. 2006). These studies predated the commissioning of EIS and other functional teams, relying on case ascertainment through general mental health services. Both ELFEP and AESOP calculated age- and sex-standardized rates using direct standardization to the population of England estimated from the 2001 Census. We used the same standard population to calculate standardized rates for our study so as to facilitate comparisons, analyses being restricted to the age range of 18–34 years, common to the three studies (ELFEP, AESOP CAMEO). Given that the incidence of psychosis in the UK has been shown to be elevated in more urban and deprived areas (Kirkbride *et al*. 2006), we expected age- and sex-standardized rates in South Cambridgeshire to be significantly lower than our reference studies.

Statistical methods

Incidence per 100 000 person-years was calculated with 95% confidence intervals (CIs). Incidence rate ratios (IRRs) were calculated (with 95% CIs) using Poisson regression to control for possible confounding. We conducted a sensitivity analysis on subjects with missing ethnicity data by repeating the Poisson regression four times, assuming all such subjects belonged to the white British, non-British white, black and other ethnic groups in turn. The likelihood ratio test (LRT) was applied to assess statistical interactions and model fit. Modelling was conducted in Stata Version 9 (Stata Corporation, USA).

Results

We identified 294 subjects aged 17–35 years who potentially met inclusion criteria for the study. Five subjects (1.7%) did not meet diagnostic criteria for psychosis, and a further four subjects (1.4%) had multiple missing data items and were excluded, leaving a sample of 285 from 569 921 person-years of follow-up (Table 1). The median age-at-contact in our sample was 22 years for both men and women. People with psychosis tended to be younger than our population at-risk. Men were over-represented among our cases (Table 1), but initial inspection of the data did not suggest differences by ethnicity, although 13 subjects (4.6%) were missing ethnicity data (see sensitivity analysis).

Incidence rates of psychosis

The overall crude incidence in our sample was 50.0 per 100 000 person-years (95% CI 44.5–56.2). Rates were higher for men than women (IRR 2.0, 95% CI 1.5–2.5), after adjustment for age and ethnicity, but declined for both sexes with increasing age (see Fig. 1). Rates in men were significantly higher than for women until 25–29 years, but we did not observe a statistically significant interaction between age and sex in our model (LRT $p=0.79$). For both men ($\lambda=124.5$, 95% CI 96.1–161.4) and women ($\lambda=49.8$, 95% CI 30.8–76.1), the highest crude incidence of psychosis was in the youngest age group (17–19 years). There was no evidence to suggest the overall incidence of psychosis changed over our 6-year period following adjustment

Table 2. *Incidence rate ratios (IRRs) by ethnicity and sex*

	All cases		Men		Women	
Ethnic group	*n* (%)	IRR (95% CI)[a]	*n* (%)	IRR (95% CI)[b]	*n* (%)	IRR (95% CI)[b]
Total	285 (100.0)		196 (100.0)		89 (100.0)	
White British	206 (72.3)	1.0	143 (73.0)	1.0	63 (70.8)	1.0
White non-British	28 (9.8)	1.1 (0.8–1.7)	17 (8.7)	1.0 (0.6–1.7)	11 (12.4)	1.4 (0.7–2.6)
Black	11 (3.9)	2.1 (1.1–3.8)	6 (3.1)	1.7 (0.7–3.8)	5 (5.6)	2.8 (1.1–7.1)
Mixed and Other	27 (9.5)	0.9 (0.6–1.4)	19 (9.7)	0.9 (0.6–1.5)	8 (9.0)	0.8 (0.4–1.8)
Unknown	13 (4.6)		11 (5.6)		2 (2.2)	

CI, Confidence interval.
[a] Adjusted for age and sex.
[b] Adjusted for age.

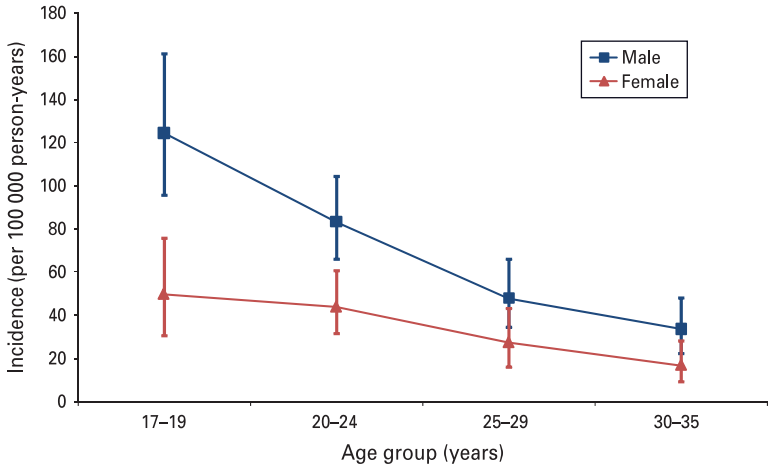


Fig. 1. Crude incidence of all psychotic disorders by age and sex, per 100 000 person-years.

for age and sex, or after taking into account possible changes to the denominator population over time (IRR 1.0, 95% CI 0.9–1.1).

After adjustment for age and sex, the incidence of psychotic disorders was significantly raised among people of black ethnicity (IRR 2.1, 95% CI 1.1–3.8) compared with the white British group (Table 2), but no other ethnic minority group was observed to have elevated rates of psychosis. We conducted a sensitivity analysis to consider whether subjects with missing data on ethnicity ($n=13$) could have affected our results. When all subjects with missing ethnicity data were recoded as white British, the raised incidence in the black group persisted (IRR 2.0, 95% CI 1.1–3.6), after adjustment for age and sex. When we assumed these subjects were from a black ethnic group, the size of this effect increased among men (IRR 4.8, 95% CI 2.9–8.0) and women (IRR 4.0, 95% CI 1.8–8.7). Full data are available from the authors.

Comparison with previous English studies of FEP

Figure 2 shows crude and directly standardized incidence rates of psychosis in our sample compared with those for the same age groups (18–34 years) from the four centres in the AESOP and ELFEP studies. We excluded 37 cases from our sample because they were aged either 17 or 35 ($n=27$; 73.0%) or because data on ethnicity were missing ($n=10$; 27.0%), leaving a sample of 248 subjects. The crude and age- and sex-standardized rates in our sample were comparable to those in Nottingham and Bristol but significantly lower than in Southeast and East London (Fig. 2). With additional standardization for ethnicity, the incidence of psychosis became non-significantly different across all catchment areas, suggesting that the excess incidence in London may be attributable to the greater proportion of black and minority ethnic (BME) groups living in the more urban areas. Accordingly, when we repeated this analysis for the white British group only,

© Cambridge University Press 2010. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <http://creativecommons.org/licenses/by-nc-sa/2.5/>. The written permission of Cambridge University Press must be obtained for commercial re-use.

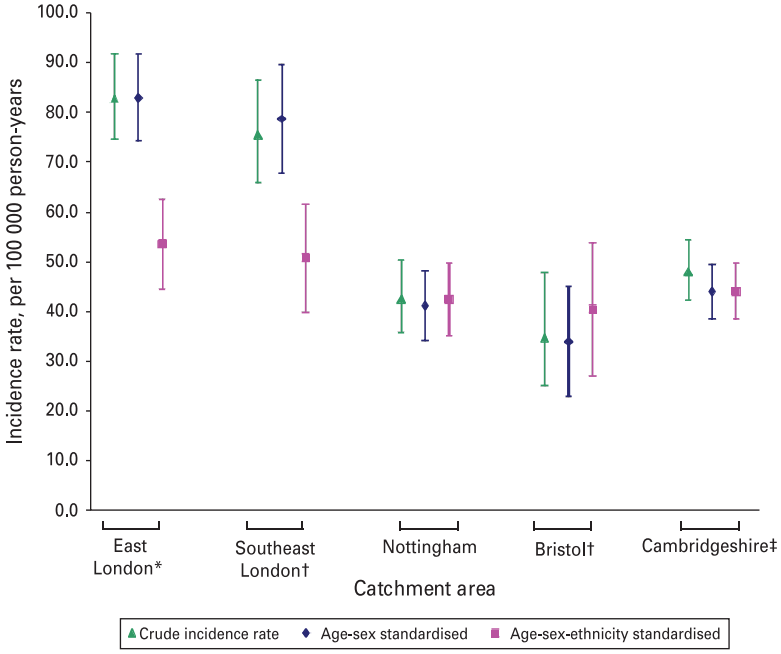


Fig. 2. Comparison of crude and directly standardized incidence rates in Cambridgeshire and four catchment areas of the AESOP and ELFEP studies (directly standardized to the population, aged 18–34 years, of England estimated in the 2001 Census). * Data made available from the authors (Coid *et al*. 2008). † Data made available from the authors (Kirkbride *et al*. 2006). ‡ Data from the present study.

we found that the crude and age- and sex-standardized incidence rates from the Cambridgeshire EIS were similar to those from the more urban London settings (Fig. 3).

Discussion

Principal findings

To our knowledge this is the first epidemiologically-based study to estimate the incidence of FEP observed through the lens of an EIS, targeting this broad diagnostic group. These administrative rates are higher than originally anticipated when EIS were commissioned in England (Department of Health, 2001), and are similar to those measured by recent observational epidemiological research in substantially more urban settings such as East and Southeast London, Nottingham or Bristol, which predate the introduction of EIS in England. We demonstrated an increased risk of psychosis among people of black ethnicities, after adjusting for sex and age, although this effect was smaller than in other studies (Fearon *et al*. 2006).

Methodological considerations

Systematic errors in either our numerator or denominator data could have led us to under- or overestimate our incidence rates, although we went to considerable lengths to minimize such issues. Regarding the numerator, our study identified a clinical sample meeting criteria for FEP detected through an EIS covering a tightly defined epidemiological catchment area over a 6-year period. Cases were ascertained on the basis of diagnoses made using standardized clinical assessments of mental state (PANSS), providing a pragmatic estimate of the psychotic morbidity in our population. We were unable to establish research diagnoses for our sample but all subjects experienced clinically relevant psychotic phenomena (delusion, hallucination, thought disorder or manic syndrome), navigated the referral process and were deemed to be in need of care from secondary mental health services, having met clinical thresholds for specified ICD-10 criteria within the F10–39 range. We did not consider specific psychotic disorders because EIS deliberately avoid diagnostic classification at service entry to accommodate the dynamic phenomenology seen in this setting and to avoid stigma; this is a weakness from the point of view of research and comparability with other studies that could be addressed in future work. However, we can be certain that our results are not due to the inclusion of false-positive cases; that is, people with subclinical ARMS, such as those identified in the general, non-clinical population, who have uncertain predictive value in terms of future psychotic disorder and associated morbidity (Bosanac *et al*. 2010). Neither funded nor designed to accommodate people with ARMS, our EIS deliberately screened out

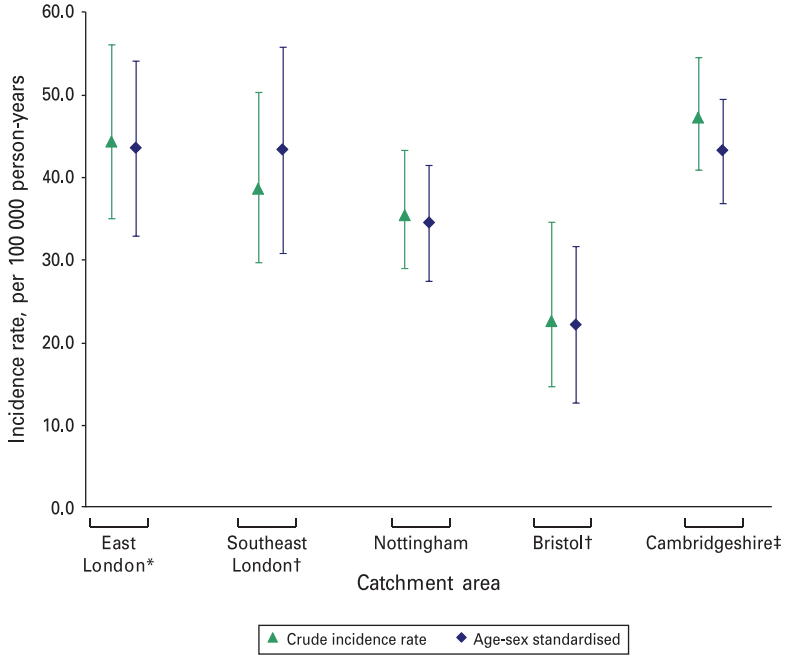


Fig. 3. Comparison of crude and directly standardized incidence rates for the white British group in Cambridgeshire and four catchment areas of the AESOP and ELFEP studies (directly standardized to the population, aged 18–34 years, of England estimated in the 2001 Census). * Data made available from the authors (Coid *et al*. 2008). † Data made available from the authors (Kirkbride *et al*. 2006). ‡ Data from the present study.

any such cases, which were subsequently referred to other parts of the health system. Our results are not due to the systematic recruitment of subjects who would have been excluded from previous epidemiological studies, such as those organized by the WHO (Jablensky & Sartorius, 2008), or our reference cohorts that took the same approach as we did to subjects with psychotic illness in the presence of drug misuse.

We did not conduct a formal leakage study, whereby efforts are made to identify people with FEP missed during the original case ascertainment period, but we made considerable routine and ongoing efforts to ensure that case ascertainment was as complete as possible. The CAMEO early intervention service is one of the longest established and epidemiologically complete EIS in England (Barnett *et al*. 2005), with plaudits for its quality. As such, it has regular contact with all major service bases in the region and invests considerable time and resources in developing and sustaining contact with primary care, educational establishments and other service bases. There was no evidence that incidence rates increased over the study period, which would otherwise have suggested that the service was not fully optimized at inception. Furthermore, if we had been missing true positive cases our results would be an underestimate of the true effect. The crude incidence of psychotic disorders in our sample was, in fact, higher than would be expected for a less deprived, predominantly rural area, the rates being comparable to those reported previously in more urban settings (Kirkbride *et al*. 2006). We note that both these potential ascertainment biases (false-positive cases and exclusion of true positives) would tend to negate each other; we have no reason to believe that either was substantial, if present at all, and are confident that they do not explain our findings.

We used annual mid-term census population data to estimate the denominator population. This method more accurately captured changes in the population at-risk over recent years than using data from the 2001 Census, which may have inflated the true incidence rates of psychosis, given an estimated increase in the denominator population between 2001 and 2007 of 6.6% (from 129 390 to 137 950) (ONS, 2001, 2009*b*). These changes was largely driven by net increases in immigration to East Anglia following EU expansion in 2004 (ONS, 2009*b*). Our mid-term population estimates would have included students in the usual resident population of Cambridge according to census methodology (ONS, 2004), ensuring that we did not underenumerate this important group in the age-at-risk. In general, we adopted an inclusive approach to estimating the denominator, a conservative approach that would tend to underestimate the true incidence of psychotic disorder in our population.

The size of our sample limited our ability to detect differences in incidence rates across ethnic groups. Nevertheless, as in previous research (Fearon *et al*.

© Cambridge University Press 2010. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <http://creativecommons.org/licenses/by-nc-sa/2.5/>. The written permission of Cambridge University Press must be obtained for commercial re-use.

2006; Kirkbride *et al*. 2008*b*), we observed elevated rates of psychosis among people of black ethnicities, effects that persisted when we tested the assumption that people missing ethnicity data were from the white British baseline group. The magnitude of risk in our study was lower than previously estimated for these groups, but we are cautious in our interpretation given the small sample size. Despite our efforts to obtain complete case ascertainment, we cannot exclude the possibility that difficult-to-reach groups that do not fully engage with mental health services may be an explanation for the lower excess risk of psychosis in BME groups in our sample. Self-reported ethnicity is the preferred method of ascribing ethnicity and we have no reason to suspect that this would have led to substantial misclassification, particularly given the relatively homogeneous ethnicity of our study population.

We controlled for age, sex and calendar year in our analyses but acknowledge that other factors, including individual-level socio-economic status or neighbourhood-level socio-economic deprivation, may have confounded our findings and provided additional sources of variation important for health service planning. Our population may differ from other UK settings, but considerable heterogeneity in Cambridgeshire exists with respect to ethnic composition and socio-economic deprivation with some very poor rural communities in the Fenland area. Unfortunately, we did not have access to socio-environmental data for the present sample but we have established a new survey throughout the Eastern region of England, the Social Epidemiology of Psychoses in East Anglia (SEPEA) study, to address this.

Overall, Cambridgeshire is less deprived, urban and ethnically heterogeneous than many English areas. Based on what is known about the epidemiology of psychosis, it would be reasonable to expect that the incidence of psychotic disorder in our population would be lower than in more urban, deprived populations. Unfortunately, we were unable to compare incidence rates presented here with those in our study population prior to the start of the CAMEO service because no routine incidence data were available at that time. This would represent the gold standard to determine whether EIS does identify excess morbidity, and we acknowledge this limitation. Nevertheless, our results are consistent with this assertion, whether compared with rates anticipated by commissioners or compared with previous empirical observations (Kirkbride *et al*. 2006; Coid *et al*. 2008). Our results should therefore be important for health-care planners and commissioners, although further EIS research in larger, urban settings will help to clarify whether other EIS are similarly inundated.

Interpreting our findings

The fact that the same sociodemographic determinants of incidence, such as age, gender and ethnicity, were apparent in our suburban and rural population as found in more urban settings is of theoretical importance. It indicates that these factors do not account for the 'urbanicity' effect found for schizophrenia and are independent of the determinants of that factor. Ethnicity, in particular, seems to modify risk regardless of urban or rural setting, supporting the notion of the risk being altered by stress-related factors associated with the psychological and cultural environment, such as discrimination, or by other classes of person–environment interaction such as exposure to novel physical toxins, infections or vitamin deficiency (see Kirkbride & Jones, 2010, for a review). Of note, in other studies high overall incidence rates of psychoses in London seemed to be directly attributable to the greater proportion of BME groups in these areas (Allardyce *et al*. 2001).

The crude incidence rates presented from this EIS were more than three times higher than anticipated by the original service planning estimates (Department of Health, 2001). It is likely that part of this discrepancy comes from the fact that, hitherto, there has been little evidence on incidence in rural settings compared with urban areas, such that the assumptions about overall rates in the general population have simply been wrong. Further evidence from more inclusive studies will address this. We have argued that our relatively high rates are not due to the inclusion of false-positive cases and ARMS. It is feasible that, set up as specialist teams, EIS are particularly effective in eliciting referrals of true positives and engaging them long enough for assessments to be made. That said, the fact that we did not have a formal leakage study, as was undertaken in our comparison samples, suggests to us that those studies and general mental health services did not massively underestimate morbidity. Another possible reason for more rural areas to look like cities could be the uniformly high prevalence of cannabis use by young people in the UK. The association between cannabis and psychosis incidence is certainly complex (Moore *et al*. 2007), and analysis of secular trends that are relatively static over recent years (Frisher *et al*. 2009) does not support the notion that the saturation of rural areas and also urban areas has led the former to behave more like the latter in terms of these illnesses.

The most obvious reason for the discrepancy between our data and the figures for EIS planning used in England (around 15 per 100 000 person-years) is that the latter are predicated largely on the incidence of schizophrenia whereas we know that only around

one-third of first-onset psychotic illness is classified as such at first presentation (Kirkbride *et al*. 2006), although there is a net evolution towards that diagnostic category over the first 3 years and beyond (Amin *et al*. 1999). Furthermore, the incidence of psychosis is higher in young adults than in the population as a whole, and EIS are targeted at the former group.

We are left with the conclusions that the incidence of psychotic illness in our mixed urban–rural catchment is fairly similar, on average, to highly urban cities, and that there is variation within all settings according to sociodemographic variables. Ethnic origin from a visibly different migrant community is a potent indicator of risk regardless of crude population setting but is influenced by factors more proximal to the individual, such as ethnic density and assimilation (Kirkbride *et al*. 2008*a*). Combined with other factors, not least those genetic and environmental entities that are associated with sociodemographic characteristics and that, themselves, modify risk, these data are further evidence of the complex eco-epidemiology of psychosis (March *et al*. 2008). We know that any urban–rural effect on administrative incidence is likely to be non-linear (Croudace *et al*. 2000), with pockets of extremely high incidence of non-affective psychosis in some neighbourhoods juxtaposed with average areas. There needs to be a high degree of granularity in any picture of the occurrence of psychosis, whether this concerns causation in a bio-psycho-social model or the health needs of the population used to plan services. Regardless of whether the field decides that functional specialization in mental health services in general, and in EIS in particular, has value and should be preserved, we urge those who make decisions about the mental health needs of populations to be aware of the devil in the detail.

Acknowledgements

The CAMEO service provided by the Cambridgeshire and Peterborough Foundation Trust is funded by the Cambridgeshire Primary Care Trust. CAMEO hosts research funded by the National Institute for Health Research (NIHR programme grant RP-PG-0606-1335), the Wellcome Trust and the Medical Research Council (MRC), and has previously hosted research funded by the Stanley Medical Research Institute and GlaxoSmithKline. J.B.K. was supported by a Sir Henry Wellcome Research Fellowship from the Wellcome Trust (grant code: WT085540 for SEPEA).

Declaration of Interest

E.T.B. is employed half-time by the University of Cambridge and half-time by GlaxoSmithKline (GSK), and he holds shares in GSK and the Brain Resource Company. P.B.J. directs the NIHR CLAHRC for Cambridgeshire and Peterborough.

References

Allardyce J, Boydell J, Van Os J, Morrison G, Castle D, Murray RM, McCreadie RG (2001). Comparison of the incidence of schizophrenia in rural Dumfries and Galloway and urban Camberwell. *British Journal of Psychiatry* **179**, 335–339.

Amin S, Singh SP, Brewin J, Jones PB, Medley I, Harrison G (1999). Diagnostic stability of first-episode psychosis. Comparison of ICD-10 and DSM-III-R systems. *British Journal of Psychiatry* **175**, 537–543.

Barnett JH, Sahakian BJ, Werners U, Hill KE, Brazil R, Gallagher O, Bullmore ET, Jones PB (2005). Visuospatial learning and executive function are independently impaired in first-episode psychosis. *Psychological Medicine* **35**, 1031–1041.

Barnett JH, Werners U, Secher SM, Hill KE, Brazil R, Masson K, Pernet DE, Kirkbride JB, Murray GK, Bullmore ET, Jones PB (2007). Substance use in a population-based clinic sample of people with first-episode psychosis. *British Journal of Psychiatry* **190**, 515–520.

Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, le Quach P, Christensen TO, Krarup G, Jorgensen P, Nordentoft M (2008). Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Archives of General Psychiatry* **65**, 762–771.

Bosanac P, Patton GC, Castle DJ (2010). Early intervention in psychotic disorders: faith before facts? *Psychological Medicine* **40**, 353–358.

Coid JW, Kirkbride JB, Barker D, Cowden F, Stamps R, Yang M, Jones PB (2008). Raised incidence rates of all psychoses among migrant groups: findings from the East London first episode psychosis study. *Archives of General Psychiatry* **65**, 1250–1258.

Craig TKJ, Garety P, Power P, Rahaman N, Colbert S, Fornells-Ambrojo M, Dunn G (2004). The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *British Medical Journal* **329**, 1067–1060.

Croudace TJ, Kayne R, Jones PB, Harrison GL (2000). Non-linear relationship between an index of social deprivation, psychiatric admission prevalence and the incidence of psychosis. *Psychological Medicine* **30**, 177–185.

Department of Health (2001). *Mental Health Policy Implementation Guide*. National Health Service: London.

Fearon P, Kirkbride JB, Morgan C, Dazzan P, Morgan K, Lloyd T, Hutchinson G, Tarrant J, Lun Alan Fung W, Holloway J, Mallett R, Harrison G, Leff J, Jones PB, Murray RM (2006). Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. *Psychological Medicine* **36**, 1541–1550.

© Cambridge University Press 2010. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence <http://creativecommons.org/licenses/by-nc-sa/2.5/>. The written permission of Cambridge University Press must be obtained for commercial re-use.

Frisher M, Crome I, Martino O, Croft P (2009). Assessing the impact of cannabis use on trends in diagnosed schizophrenia in the United Kingdom from 1996 to 2005. *Schizophrenia Research* **113**, 123–128.

Grawe RW, Falloon IRH, Widen JH, Skogvoll E (2006). Two years of continued early treatment for recent-onset schizophrenia: a randomised controlled study. *Acta Psychiatrica Scandinavica* **114**, 328–336.

Jablensky A, Sartorius N (2008). What did the WHO studies really find? *Schizophrenia Bulletin* **34**, 253–255.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Kirkbride JB, Boydell J, Ploubidis GB, Morgan C, Dazzan P, McKenzie K, Murray RM, Jones PB (2008*a*). Testing the association between the incidence of schizophrenia and social capital in an urban area. *Psychological Medicine* **38**, 1083–1094.

Kirkbride JB, Coid JW, Barker D, Cowden F, Stamps R, Yang M, Jones PB (2008*b*). Psychoses, ethnicity and socio-economic status. *British Journal of Psychiatry* **193**, 18–24.

Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AESOP study. *Archives of General Psychiatry* **63**, 250–258.

Kirkbride JB, Jones PB (2010). The prevention of schizophrenia – what can we learn from eco-epidemiology? *Schizophrenia Bulletin*. Published online: 25 October 2010. doi:10.1093/schbul/sbq120.

Kuehn BM (2010). Early interventions for schizophrenia aim to improve treatment outcomes. *Journal of the American Medical Association* **304**, 139–145.

Lester H, Birchwood M, Bryan S, England E, Rogers H, Sirvastava N (2009). Development and implementation of early intervention services for young people with psychosis: case study. *British Journal of Psychiatry* **194**, 446–450.

March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, Susser E (2008). Psychosis and place. *Epidemiologic Reviews* **30**, 84–100.

Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry* **62**, 975–983.

Marshall M, Rathbone J (2008). Early intervention for psychosis. *Cochrane Database of Systematic Reviews*, 18, CD004718.

McGorry P, Johanessen JO, Lewis S, Birchwood M, Malla A, Nordentoft M, Addington J, Yung A (2010). Early intervention in psychosis: keeping faith with evidence-based health care. *Psychological Medicine* **40**, 399–404.

McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ (1996). EPPIC: an evolving system of early detection and optimal management. *Schizophrenia Bulletin* **22**, 305–326.

McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine* **2**, 13.

Mihalopoulos C, Harris M, Henry L, Harrigan S, McGorry P (2009). Is early intervention in psychosis cost-effective over the long term? *Schizophrenia Bulletin* **35**, 909–918.

Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319–328.

Noble M, McLennan D, Wilkinson K, Whitworth A, Barnes H, Dibben C (2008). *The English Indices of Deprivation 2007*. Communities and Local Government: London.

ONS (2001). *Census 2001*. Office for National Statistics (http://www.ons.gov.uk/census/get-data/index.html). Accessed 29 December 2009.

ONS (2004). *Census 2001 Definitions*. The Stationery Office: London.

ONS (2009*a*). *Population Estimates by Ethnic Group Methodology Paper*. Office for National Statistics: Newport.

ONS (2009*b*). Table 8 – Mid-2007 UK, England and Wales, Scotland and Northern Ireland population estimates. In *Population Estimates for UK, England and Wales, Scotland and Northern Ireland – Current Datasets*. Office for National Statistics: Fareham.

Pelosi AJ, Birchwood M (2003). Is early intervention for psychosis a waste of valuable resources? *British Journal of Psychiatry* **182**, 196–198.

Appendix 2 Psychosis incidence through the prism of early intervention services

BJPsych The British Journal of Psychiatry (2012) 200, 156–157. doi: 10.1192/bjp.bp.111.094896

Short report

Psychosis incidence through the prism of early intervention services

J. B. Kirkbride, C. Stubbins, P. B. Jones

Summary
We know little about first-episode psychosis epidemiology beyond cities or when measured through early intervention in psychosis services. We present results from 18 months of the 3-year Social Epidemiology of Psychoses in East Anglia (SEPEA) study of incepted incidence observed through five early intervention services. We identified 378 eligible individuals (incidence: 45.1/100 000 person-years, 95% CI 40.8–49.9). Rates varied across these services, but were 2–3 times higher than those on which services were commissioned. Risk decreased with age, was nearly doubled among men and differed by ethnic group; doubled in people of mixed ethnicity but lower for those of Asian origin, compared with White British people. Psychosis risk among ethnic minorities was lower than reported in urban settings, which has potential implications for aetiology. Our data suggest considerable psychosis morbidity in diverse, rural communities.

Declaration of interest
None.

Research into social factors in the aetiology of psychotic disorders has demonstrated notable variation observed by age and gender,[1] cannabis use,[2] immigrant status and ethnicity,[3] and urban birth and upbringing.[4] This epidemiological landscape is taken from studies predominately conducted in large cities.[4] Less is understood about these risk markers outside of conurbations, where almost one-fifth of the English population lives.[5] Delineating such epidemiology is also relevant to health services planning, particularly given recent reports that early intervention in psychosis services in both urban and rural English communities have observed psychosis rates up to three times higher than those upon which such services were first commissioned (i.e. 15/100 000 person-years).[6,7] We present initial findings from the Social Epidemiology of Psychoses in East Anglia (SEPEA; www.sepea.org) study, a large, 3-year population-based first-episode psychoses study.

Method

The study methodology was based on the principles of a major epidemiological study of first-episode psychosis previously conducted in England,[1] modified for use in early intervention services. We established a surveillance system to record socio-demographic and clinical data on all people aged 16–35 years resident within East Anglia, referred and accepted to our early intervention services with first-episode psychosis over 3 years, from 1 August 2009. ICD-10 clinical and research (OPCRIT) diagnoses for psychotic disorder (F10-39) are established at 6 months and 3 years after referral. Here, we report sample characteristics and initial incidence rates from the first 18 months of case ascertainment, using 2009 mid-term census population estimates as the denominator, adjusted for study duration. Poisson regression (Stata, version 11) explored covariate effects. Full method is given in the online supplement.

Results

Over the first 18 months of the study 510 people were referred to early intervention services in East Anglia with suspected first-episode psychosis. In total 70% ($n = 357$) met inclusion criteria during over 835 000 person-years of follow-up. The main reason for exclusion was not meeting clinical criteria for psychosis at referral ($n = 106$; 20.8%) (see online Fig. DS1 for a complete breakdown of exclusions).

The crude incidence of clinically relevant psychotic disorder in East Anglia was estimated as 42.6/100 000 person-years (95% CI 38.4–47.2). Rates were generally similar across services (online Table DS1), but were notably raised in Great Yarmouth and Waveney (54.9/100 000 person-years; 95% CI 39.9–75.4). Completed demographic data were available on 357 individuals (92.4%) at the time of analysis. Median age at first presentation was similar for women (21.9 years, IQR = 18.2–25.8) and men (22.3 years, IQR = 19.3–26.7). Risk was elevated among men (RR = 1.7, 95% CI 1.4–2.2), after adjustment for age and ethnicity. Our data also suggested risk differed by ethnicity. Compared with the White British group, people of Black (RR = 1.8; 95% CI 1.0–3.3) and mixed ethnicities (RR = 2.1; 95% CI 1.3–3.6) were at elevated risk of psychotic disorder after adjustment for age and gender. By contrast, people of Asian origin (including the Indian subcontinent and Southeast Asia) were at lower risk of psychosis compared with the White British group (adjusted RR = 0.5, 95% CI 0.3–0.9) (Table 1).

A total of 50% of our sample were unemployed at initial referral; 25% were in paid employment, 19% were students and 4% were unpaid family carers; information was missing from 2% of our sample.

Discussion

We identified variation in the incidence of psychosis in a diverse, mainly rural English region. The overall incidence was higher than typically reported in first-episode psychosis studies of the entire adult age range (16–64 years), but this is to be expected given our lower age limit (35 years) and the decline in risk with age.[1] For comparison, the incidence for people 16–35 years old in the ÆSOP study varied from 32.0/100 000 person-years in Bristol to 74.0/100 000 person-years in south-east London, placing our estimates within this range. Nevertheless, observations from both SEPEA and ÆSOP are consistent with recent empirical data[7] that the incidence of psychotic disorders seen through early intervention services is generally three times greater than the figure upon which such services were commissioned.[6] This has

© Royal College of Psychiatrists. This paper accords with the Wellcome Trust Open Access policy and is governed by the licence available at http://www.rcpsych.ac.uk/pdf/Wellcome%20Trust%20licence.pdf.

Table 1 Sample characteristics and adjusted rate ratios in the SEPEA study at 18 months[a]

Variable	Participants, *n* (%)	Denominator, *n* (%)[b]	Adjusted[c] relative risk (95% CI)
Total	357 (100)	838 574 (100)	–
Early intervention service (*n* = 357)			
Cambridgeshire, Peterborough & Royston	122 (34.2)	306 283 (36.5)	–
West Norfolk	17 (4.8)	41 765 (5.0)	–
Central Norfolk	91 (25.5)	219 860 (26.2)	–
Great Yarmouth & Waveney	38 (10.6)	69 218 (8.3)	–
Suffolk	89 (24.9)	201 448 (24.0)	–
Gender (*n* = 330)			
Women	115 (34.8)	405 221 (48.3)	1
Men	215 (66.2)	433 353 (51.7)	1.7 (1.4–2.2)
Age group (*n* = 330)			
16–17	52 (15.8)	71 929 (8.6)	1
18–19	53 (16.1)	88 976 (10.6)	0.8 (0.6–1.2)
20–24	118 (35.8)	219 157 (26.1)	0.7 (0.5–1.0)
25–29	73 (22.1)	213 385 (25.4)	0.5 (0.3–0.7)
30–35	34 (10.3)	245 127 (29.2)	0.2 (0.1–0.3)
Ethnicity (*n* = 330)			
White British	261 (79.1)	671 588 (80.1)	1
White non-British	21 (6.4)	50 882 (6.1)	1.2 (0.8–1.9)
Mixed ethnicity	15 (4.5)	17 364 (2.1)	2.1 (1.3–3.6)
Black	12 (3.6)	18 471 (2.2)	1.8 (1.0–3.3)
Asian	12 (3.6)	69 014 (8.2)	0.5 (0.3–0.9)
Other ethnicities	9 (2.7)	11 255 (1.3)	2.3 (1.2–4.5)

a. Because the study is ongoing, detailed sociodemographic data were only available for a subset (*n* = 309) of the total incidence sample (*n* = 378). Thus, incidence rates were reported where we had data on the full sample (*n* = 378), with relative risks reported from Poisson regression on demographic data for the subsample (*n* = 309).
b. Adjusted for duration of case ascertainment in each early intervention service (18 months).
c. Adjusted for other variables in model (age group, gender and ethnicity).

important implications for mental health service provision. In our sample, age at first presentation was similar for both genders before 36 years old, a point easily overlooked in entire adult-onset samples, where median age at onset typically occurs a few years later for women[1] as a result of a secondary peak of psychosis close to the time of menopause,[8] not captured by our early intervention services data.

We also reported elevated psychosis risk for some minority groups in East Anglia, although not, even at the upper limit of the confidence interval, to the extent observed in more urban settings.[3] Strikingly, relative risk estimates in people from Asian populations were half those observed in the White British group. Although we cannot exclude the possibility that these differences were explained by differential service utilisation, our findings are consistent with the possibility that migrant and minority groups in more rural communities may not be exposed to the same degree to the factors that drive elevated psychosis rates in cities. This hypothesis will be pursued in the full data-set, but there is already supporting evidence: cumulative social disadvantage and separation and loss events in childhood are reported to be associated with increased odds of psychosis for both White British and ethnic minority groups but the impact of such events appears to be more pervasive among some minority groups.[9,10] If socioenvironmental exposures were also amplified in urban compared with rural populations, or led to greater stress responses in urban dwellers, as has been recently observed in a small sample of healthy adults,[11] this could potentially explain the attenuation in elevated rates among rural minority populations.

Our initial data suggested that incidence rates were elevated in one of our services, and we will consider multivariate, multilevel explanations for this in our final data-set, including the possibility that the variation may be partially driven by service-side factors, such as the degree of active outreach provided by different services and the length of time services have been established. We will also be able to inspect differences in rates according to diagnostic subgroup and demographic factors not reported here (including country of birth, age at migration, generation status, occupation), compare clinical- and research-based diagnoses, and inspect the evolution of symptomatology in a first-episode sample over 3 years of treatment. Nevertheless, the incepted incidence rates assessed here through clinical early intervention services highlight a substantial burden of psychotic disorder beyond cities, and potentially provide important aetiological clues.

J. B. Kirkbride, PhD, **C. Stubbins**, BA(Hons), **P. B. Jones**, PhD, MRCPsych, Department of Psychiatry, University of Cambridge, Cambridge, UK

Correspondence: J. B. Kirkbride, Department of Psychiatry, University of Cambridge, Box 189, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. Email: jbk25@cam.ac.uk

First received 29 Mar 2011, final revision 15 Jul 2011, accepted 28 Jul 2011

Funding

J.B.K. was supported by a Sir Henry Wellcome Research Fellowship from the Wellcome Trust (grant number WT085540), through which the SEPEA study was established. P.B.J. directs the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for Cambridgeshire & Peterborough and is supported by NIHR grant RP-PG-0606-1335. The SEPEA study has been adopted by the Mental Health Research Network (MHRN).

Acknowledgements

The authors are grateful to the clinical services and staff participating in the SEPEA study, and the MHRN for their generous support.

References

1 Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center ÆSOP Study. *Arch Gen Psychiatry* 2006; **63**: 250–8.

2 Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; **370**: 319–28.

3 Cantor-Graae E, Selten J-P. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry* 2005; **162**: 12–24.

4 March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, et al. Psychosis and place. *Epidemiol Rev* 2008; **30**: 84–100.

5 Department for Environment, Food and Rural Affairs. *Statistical Digest of Rural England 2011*. DEFRA, 2011.

6 Department of Health. *Mental Health Policy Implementation Guide*. National Health Service, 2001.

7 Cheng F, Kirkbride JB, Lennox BR, Perez J, Masson K, Lawrence K, et al. Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting. *Psychol Med* 2011; **41**: 949–58.

8 Grigoriadis S, Seeman MV. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. *Can J Psychiatry* 2002; **47**: 437–42.

9 Morgan C, Kirkbride J, Hutchinson G, Craig T, Morgan K, Dazzan P, et al. Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. *Psychol Med* 2008; **38**: 1701–15.

10 Morgan C, Kirkbride JB, Leff J, Hutchinson G, McKenzie K, Morgan K, et al. Parental separation, loss and psychosis in different ethnic groups: a case-control study. *Psychol Med* 2007; **37**: 495–503.

11 Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature* 2011; **474**: 498–501.

OPEN ACCESS EXTRA CONTENT ONLINE

Appendix 3 A population-level prediction tool for the incidence of first-episode psychosis: translational epidemiology based on cross-sectional data

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

Open Access Research

BMJ open accessible medical research

A population-level prediction tool for the incidence of first-episode psychosis: translational epidemiology based on cross-sectional data

James B Kirkbride,[1] Daniel Jackson,[2] Jesus Perez,[3] David Fowler,[4] Francis Winton,[5] Jeremy W Coid,[6] Robin M Murray,[7] Peter B Jones[1,8]

To cite: Kirkbride JB, Jackson D, Perez J, *et al*. A population-level prediction tool for the incidence of first-episode psychosis: translational epidemiology based on cross-sectional data. *BMJ Open* 2013;**3**: e001998. doi:10.1136/bmjopen-2012-001998

▸ Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-001998).

Received 23 August 2012
Revised 21 December 2012
Accepted 21 December 2012

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see http://bmjopen.bmj.com

For numbered affiliations see end of article.

Correspondence to
Dr James Kirkbride;
jbk25@cam.ac.uk

ABSTRACT

Objectives: Specialist early intervention services (EIS) for people aged 14–35 years with first episodes of psychosis (FEP) have been commissioned throughout England since 2001. A single estimate of population need was used everywhere, but true incidence varies enormously according to sociodemographic factors. We sought to develop a realistically complex, population-based prediction tool for FEP, based on precise estimates of epidemiological risk.

Design and participants: Data from 1037 participants in two cross-sectional population-based FEP studies were fitted to several negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at-risk of a third, socioeconomically different region to predict expected caseload over 2.5 years, where the observed rates of ICD-10 F10-39 FEP had been concurrently ascertained via EIS.

Setting: Empirical population-based epidemiological data from London, Nottingham and Bristol predicted counts in the population at-risk in the East Anglia region of England.

Main outcome measures: Observed counts were compared with predicted counts (with 95% prediction intervals (PI)) at EIS and local authority district (LAD) levels in East Anglia to establish the predictive validity of each model.

Results: A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EIS in East Anglia (95% PI 459, 559), compared with 522 observed participants. This model predicted correctly in 5/6 EIS and 19/21 LADs. All models performed better than the current gold standard for EIS commissioning in England (716 cases; 95% PI 664–769).

Conclusions: We have developed a prediction tool for the incidence of psychotic disorders in England and Wales, made freely available online (http://www.psymaptic.org), to provide healthcare commissioners with accurate forecasts of FEP based on robust epidemiology and anticipated local population need. The initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.

ARTICLE SUMMARY

Article focus

- Commissioners require precise information on the health needs of their local populations to effectively plan health services.
- A failure to arm mental health commissioners with precise epidemiological data led to misestimation of actual activity in early intervention in psychosis services (EIS).
- We sought to develop a prediction tool for the incidence of first episode psychosis (FEP), by applying precise estimates of epidemiological risk in various sociodemographic groups to the structure of the population at-risk in a different region, where the observed incidence had been concurrently ascertained.

Key messages

- A model of psychosis incidence which included age, sex, ethnicity and population density yielded precise FEP predictions in our new region, outperforming the Department of Health in England's current gold standard for EIS commissioning.
- While our model provides forecasts of the burden of FEP in different populations, the initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.
- We have translated this model into a freely available prediction tool (http://www.psymaptic.org) to facilitate evidence-based healthcare commissioning of socioculturally relevant services according to local need.

BACKGROUND

Commissioners of health and social care require precise information on the health needs of their local populations,[1] especially if parity of mental and physical health is to be realised.[2] Mental health disorders alone represent the leading disease burden in the UK

© 2016 Copyright Clearance Center, Inc. All Rights Reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

ARTICLE SUMMARY

Strengths and limitations of this study

- Our modelling approach used robust epidemiological data from two large studies of first episode psychosis in England to provide estimates of incidence in a third study region, producing accurate FEP forecasts.
- While our models provide estimates of the expected clinical burden of FEP in the community, services may see a broader range of psychopathology consuming resources, or incepted rates may be influenced by supply-side organisational factors.
- Owing to data availability, it was not possible to validate our prediction tool in settings outside of England and Wales, or for specific psychotic disorders. As data become available, we will extend the capability of our prediction tool, including into other settings and disorders.

(22.8%).[3] They contribute substantially to healthcare expenditure and societal costs even before physical ill health is taken into account. The Centre for Mental Health estimated the total costs of mental health to British health services and society at £105 billion in 2009/2010,[4] a figure expected to double over the next 20 years.[2] These are serious challenges compounded by a paucity of information on which to commission appropriate services. Early intervention in psychosis services (EIS) for people aged 14–35 years with a first episode of psychosis (FEP) offer a useful example of failure to map services to local need.

EIS are a major evidence-based innovation, systematically commissioned throughout England and Wales over the past decade.[5] When EIS intervention is sustained, there is evidence that people with psychosis achieve better functional and social outcomes.[6 7] Such services are also highly cost-effective.[4 8 9] However, EIS were originally commissioned on an anticipated rate of 150 new cases of any psychotic disorder per 1 000 000 of the total population per year in the Department of Health's Mental Health Policy Implementation Guide (MH-PIG).[5] In 2001 in England and Wales, 29.3% of the population were aged 14–35 years, meaning that the MH-PIG commissioned incidence rate was approximately 51 cases/100 000 person-years in the age range covered by EIS. Following their deployment, anecdotal reports began to emerge from EIS in different regions to suggest that a uniform figure for commissioning was simultaneously underestimating[10] and overestimating[11] the actual observed need in urban and rural populations, respectively. Recent epidemiological evidence of FEP incidence in rural communities in England has suggested that rates are somewhat lower than the uniform figure upon which services were commissioned,[12 13] confirming previous calls that a 'one-size-fits-all' prescription for EIS implementation is unlikely to lead to the efficient allocation of finite mental health resources.[14 15]

Using rich epidemiological data on variation in the incidence of FEP according to major sociodemographic risk factors,[16–19] we describe the development and validation of a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder, based on the sociodemographic structure of the population in a given region. Applied to FEP as proof-of-concept, we show that it is possible to closely predict the expected incidence in a given population, where the observed count of cases was within the prediction intervals (PI) forecast by our models. We applied our most precise prediction model to the population of England and Wales to provide health commissioners with a translational epidemiological prediction tool to underpin information-based service planning.

METHODS

Our prediction models were based on epidemiological data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) and the East London First Episode Psychoses (ELFEP) studies,[18 20] two methodologically similar population-based FEP studies. We fitted various count-based regression models with different combinations of sociodemographic and socioenvironmental factors, well established in the literature to be associated with the incidence of psychotic disorder.[21 22] We first established the relative *apparent validity* of each model by estimating model-fit diagnostics to assess how well each model fitted the empirical data (henceforth, the *prediction sample*). We next sought to estimate the *external validity* of each model by applying model-based parameter coefficients to the population structure of a purposefully different region of England, East Anglia (henceforth, the *validation sample*). This out-of-sample prediction technique allowed us to obtain the expected incidence of disorder in this region forecast by each model, which we compared with observed rates simultaneously ascertained in this region via the ongoing Social Epidemiology of Psychoses in East Anglia (SEPEA) study.[13] We performed various model-fit diagnostics to identify which, if any, model demonstrated utilisable predictive capability.

Empirical data underlying prediction models (*prediction sample*)

Case ascertainment (numerator)

The designs of the ÆSOP and ELFEP studies have been described in detail elsewhere,[18 20] with features relevant to the present paper summarised here. Case ascertainment took place over 2 years in ELFEP (Newham: 1996–1998; Tower Hamlets & Hackney: 1998–2000) and the Southeast London and Nottingham centres of the ÆSOP study (1997–1999), and over the first 9 months of 1997 in Bristol (ÆSOP). All service bases were screened regularly for potential new contacts aged 16–64 years (18–64 in ELFEP) resident within these catchment areas. Leakage studies were conducted to identify participants missed by this initial screen, but meeting inclusion criteria for FEP.[18 20] All participants who received an ICD-10 F10–39 diagnosis for psychotic disorder

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

following assessment via the Schedules for Clinical Assessment in Neuropsychiatry were included in the incident sample, except those with an organic medical basis to their disorder or profound learning difficulty. Data on age-at-contact, sex and ethnicity were collected on included participants. We geocoded participants' residential postcode at first contact to their corresponding local authority district (LAD) to allow us to model possible neighbourhood effects associated with the incidence of psychotic disorder, such as population density or socioeconomic deprivation.

Population at-risk

We estimated the population at-risk using the 2001 Census of Great Britain, adjusted for study duration, and stratified by age group (16–17, 18–19, then 5-year age bands), sex and ethnicity. Ethnicity was based on self-ascription according to 1 of 10 categories derived from the census: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white and black Caribbean, other mixed ethnic backgrounds and all other ethnicities.

Socioenvironmental variable estimation

We estimated LAD-level deprivation using the 2004 Index of Multiple Deprivation (IMD) in England, which estimated domains of deprivation using measures predominantly collected close to the time of our case ascertainment periods (see table 1).[23] We z-standardised English LAD IMD scores to have a mean of zero and SD of 1, and extracted IMD z-scores for the 14 LADs in the ÆSOP and ELFEP studies. To inspect whether any particular deprivation domain was a better predictor of psychosis incidence than IMD, we also considered LAD-level income deprivation, employment deprivation and the extent of deprivation in our models (table 1). We estimated population density by dividing each LAD's usual resident population by its area (in hectares), using ArcGIS V.9.3 software.

Table 1 Description of included socioenvironmental variables*†

Variable	Classification and description
Multiple deprivation	Weighted data from routine national sources across seven domains: income, employment, education, health, barriers to housing and services, living environment, crime. Continuous, z-standardised scores for analysis
Extent of deprivation	Proportion of LAD population living in 20% most deprived SOA in England (%)
Income deprivation	Proportion of all people in LAD classified as income deprived (%)
Employment deprivation	Proportion of adults of working age in LAD classified as employment deprived (%)
Population density	Population density at LAD level (people per hectare)

*_Prediction sample_ sources: Population density—2001 census estimates; deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP and ELFEP case ascertainment periods (ie, 1997–2000).
†_Validation sample_ sources: Population density—2009 mid-year census estimates; deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to the SEPEA case ascertainment period (2008).
IMD, Index of Multiple Deprivation; LAD, local authority district; SOA, super output area.

Observed data for external validation of prediction models (*validation sample*)

Observed participants and population at-risk data for our *validation sample* were obtained from the SEPEA study, an ongoing study of the incidence of psychotic disorders incepted over 3.5 years (2009–2013) through one of six EIS covering 20 LADs and a subsection of 1 LAD (the town of Royston, Hertfordshire) in Norfolk (three EIS: West Norfolk, Central Norfolk, and Great Yarmouth and Waveney), Suffolk (one EIS) and Cambridgeshire, Royston and Peterborough (CAMEO North and South EIS).[13]

Case ascertainment

To establish the incepted incidence of FEP as seen through EIS, entry criteria for the SEPEA study were:

- Referral to an EIS in East Anglia for a suspected first episode of psychosis;
- Aged 16–35 years at first referral to EIS (17–35 years in CAMEO services);
- Resident within the catchment area at first referral;
- First referral during case ascertainment period (2009–2013).

At 6 months after EIS acceptance, or discharge from the service, whichever was sooner, we asked the clinician responsible for care to provide an ICD-10 F10–39 psychiatric diagnosis using all information available. We excluded participants without a clinical FEP diagnosis, or participants presenting with an organic basis to their disorder or profound learning disability. For the remaining participants, basic sociodemographic and postcode information was recorded and classified in the same way as in the *prediction sample*. We included participants presenting to EIS during the first 2.5 years of the ongoing SEPEA study.

Population at-risk

We estimated the population at-risk of East Anglia using 2009 mid-year census estimates published by the Office for National Statistics (ONS) at the LAD level, by age group, sex and ethnicity.[24] These estimates used the 2001 census base, adjusted for immigration, births and deaths each year. It was not possible to obtain 2009 mid-year estimates for the town of Royston, because data were only published at LAD level. Here, we used denominator data from the 2001 census data in order to

© 2016 Copyright Clearance Center, Inc. All Rights Reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

estimate the population at-risk in Royston. We do not believe that this would have substantially invalidated our results as this town represented 0.6% of the overall population at-risk (n=9555) in the SEPEA study. Denominator data were multiplied by 2.5 to account for person-years of exposure in the *validation sample*.

Socioenvironmental variable estimation

For each LAD in the SEPEA study, we obtained corresponding socioenvironmental variables to those included in our *prediction sample*, using updated data collected as close to the SEPEA case ascertainment period as possible. Population density was estimated using 2009 mid-term population estimates. Our measures of deprivation were derived from IMD 2010,[25] which was estimated in an analogous way to 2004 data, but collected from sources obtained immediately prior to the SEPEA study.

Statistical techniques

Dataset generation

We constructed a dataset for the regression analysis of count data by pooling data from the ÆSOP and ELFEP studies (the *prediction sample*). Data were stratified by age group, sex, ethnicity and LAD, such that each stratum (N=2536) represented the total count of FEP cases in a unique sociodemographic group for a given LAD, with a corresponding estimate of the population at-risk, treated as an offset in our models. Our socioenvironmental measures (population density, deprivation) were adjoined to the dataset for each LAD. Population at-risk data from the *validation sample* were stratified in the same way and retained in a separate database. Here, the count of cases, which we wished to predict, was entered as a vector of missing data which would be populated with predicted case estimates following prediction modelling.

Prediction models

We used the *prediction sample* data to fit negative binomial regression models to obtain parameter coefficients of incidence for the sociodemographic and socioenvironmental factors included in each model. We considered the internal and external predictive capabilities of six models, all of which contained age group, sex, an age–sex interaction term and ethnicity. Model 1 contained no further covariates. Model 2 also included IMD. We replaced IMD with either income, employment or the extent of deprivation, respectively, in models 3–5. Model 6 included population density. Initial exploration of the *prediction sample* data indicated the presence of possible overdispersion (variance (δ^2=1.37) exceeded mean (μ=0.4) count of cases), so negative binomial regression was preferred to Poisson regression since it explicitly models any overdispersion with an extra dispersion parameter.

Apparent model validity and prediction

We assessed apparent model validity in three ways. First, we used Akaike's Information Criterion (AIC) to assess the respective overall fit of each model to the data. Second, we conducted K-fold cross-validation to assess each model's apparent validity to predict cases within the *prediction sample*. This method randomly allocated strata in the *prediction sample* into *K* subsets. Each model was then re-estimated on K-1 subsets (the *training data*) to predict the expected counts of cases in the Kth subset (the *test data*). This was repeated over K trials, such that each stratum in the dataset appeared exactly once as the *test data*. At the end of this process, we derived Lin's concordance correlation coefficient (CCC) and 95% CI to estimate the correlation between the predicted and observed counts of cases across all strata in the *prediction sample*. Finally, we estimated the root mean squared error (RMSE) to determine the average error between fitted and observed values from each model. Lower RMSE scores indicated a smaller prediction error. The RMSE is derived as

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n} (\gamma_i - \hat{\gamma}_i)^2}{n}}$$

where γ_i and $\hat{\gamma}_i$ are the observed and predicted counts of cases in the ith stratum, respectively, and n is the number of strata.

We repeated K-fold cross-validation h times, generating K new random divisions of the data each time. We retained model-fit diagnostics across Kh iterations, and reported the mean of Lin's CCC and RMSE to provide summary cross-validation statistics for each model. We specified K=10 and h=20, as recommended for cross-validation to obtain precise model-fit diagnostics.[26]

External model prediction and validation

We retained parameter coefficients from each model (using the full *prediction sample* data) and applied these to the corresponding population at-risk in the *validation sample* dataset. This gave out-of-sample prediction estimates for the expected count of cases in each stratum of the *validation sample*, given the model. We summed expected counts across relevant strata to estimate the (1) total predicted count of cases in the SEPEA region, (2) predicted counts in each EIS and (3) predicted counts by LAD. These counts were further stratified by broad age group (16–35, 36–64 and 16–64 years). Because the census (denominator) data were unavailable for 35-year-olds alone (needed to estimate their contribution to predicted counts in the age range for EIS, 16–35 years), we assumed that the risk coefficient was the same across all ages within the 35–39-year-old age group. We apportioned predicted counts on a 1:4 ratio (35:36–39 years) to their respective broad age groups.

To determine how well the MH-PIG[5] figure of 51 new cases per 100 000 person-years for EIS performed as a

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

predictive tool, we also estimated the predicted count of cases in the *validation sample* under this scenario, which we termed 'Model 7'.

We derived 95% PIs for all summary predictions from first principles, since their derivation is not straightforward, nor routinely implemented by statistical software. PIs are similar to CIs, but account for SEs introduced in both the *prediction* and *validation* samples. We developed a bootstrap-like approach to obtain PIs from each model by simulating 1000 model-based realisations of the quantities we wished to predict, where we took the parameters to be the maximum likelihood estimates. We obtained the lower and upper bounds of the PIs as the corresponding quantiles of the simulated realisations (see appendix for full details).

To assess each model's external predictive capabilities, we considered five markers of predictive accuracy. We compared the number of times the observed count of cases in the SEPEA study fell within the PIs estimated from each model for (1) the SEPEA region, (2) at the EIS level and (3) at the LAD level. We also derived EIS-level (4) and LAD-level (5) RMSE scores to estimate prediction error from each model in our *validation sample*. We ranked model performance (1: best and 7: worst) on these five measures, and estimated an overall mean rank to determine the overall predictive validity of each model.

Observational data on first episode psychosis in our *validation sample* were not available for the age range 36–64 years, so external validation was restricted to the 16–35 year old age range. For completeness, however, we also reported the overall predicted count of cases for this age group from each model.

Extrapolation to the UK

Guided by our validation procedures, we identified which model had the greatest overall predictive validity, and proposed this as a candidate for FEP incidence prediction in England and Wales. We repeated out-of-sample prediction on the sociodemographic and socioenvironmental population characteristics of each LAD in England and Wales to obtain national-level and LAD-level predictions. Denominator data were obtained from the ONS 2009 mid-term estimates and stratified as previously described. Overall counts were derived for three broad age groups (16–35, 36–64 and 16–64 years), and for each of these, by sex and ethnicity. The 95% PIs were estimated as before. We visualised these data on maps and in tables to provide healthcare planners and commissioners with an easy-to-use tool to forecast the expected incidence of psychotic disorder in England and Wales. We have made this available as a free, open-use prediction tool, known as PsyMaptic (V.0.5) (Psychiatric Mapping Translating Innovations into Care; http://www.psymaptic.org). Counts of cases predicted by our model were compared with those obtained under the Department of Health's uniform rate in each LAD. We expressed these comparisons as ratios with 95% CIs derived using the same method as for standardised morbidity ratios (SMR). This approach was conservative because here we substituted the usual numerator in an SMR, the observed, O, for a predicted count. Unlike an observed count, no sampling variation is present for the predicted count, only uncertainty due to the model from which the prediction was estimated. Since variance in the prediction is therefore much smaller than the variance normally present for the numerator (O), this led to conservative estimates of 95% CI. Ratios in LAD where 95% CI did not span unity could therefore be interpreted as regions where there was strong evidence that the predictions from our model differed significantly from those predicted by the department of health's uniform rate.

Software

All negative binomial regression models, out-of-sample prediction and estimation of 95% PI were conducted in R (V.2.15.1). Cross-validation and model-fit diagnostics were conducted in Stata (V.11). Prediction maps for England and Wales were created using StatPlanet Plus (V.3.0) visualisation software.[27]

RESULTS

Prediction sample

Our prediction models contained data on 1037 persons with a first episode psychosis in the ÆSOP (n=553; 53.3%) and ELFEP (n=484; 46.7%) studies, ascertained from over 2.4 m person-years at-risk. Twelve participants were excluded from the original ÆSOP sample because they were of no fixed abode and could not be geocoded to an LAD.[18]

The population at-risk in the *prediction sample* came from LADs with higher median levels of multiple and employment deprivation, extent of deprivation and population density than the population at-risk in the *validation sample*, though there were no statistically significant differences in median income deprivation between the two samples (see online supplementary table S1).

Parameter coefficients obtained from the full prediction sample following negative binomial regression are shown in table 2. As previously reported from these data,[20 28] incidence rates were generally raised in ethnic minority groups compared with the white British population. Models 2–6 included a measure of LAD deprivation (models 2–5) or population density (model 6), which were all significantly associated with an increased incidence of psychotic disorder, after control for individual-level confounders. Each of these models produced a lower AIC score than a model fitted solely with individual-level covariates (model 1), indicating a better fit. Cross-validation suggested that all models achieved good CCC agreement between predicted and observed cases, with low RMSE values (table 2).

Validation sample

Observed participants

We identified 572 potential participants over the first 30 months of the SEPEA study, aged 16–35 years, who

© 2016 Copyright Clearance Center, Inc. All Rights Reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

Table 2 Prediction models, covariates and fit: all clinically relevant psychoses (F10–39)

Variable	Model 1 IRR (95% CI)	Model 2 IRR (95% CI)	Model 3 IRR (95% CI)	Model 4 IRR (95% CI)	Model 5 IRR (95% CI)	Model 6 IRR (95% CI)
Age group×sex interaction*	p=0.07	p=0.06	p=0.06	p=0.06	p=0.06	p=0.06
Ethnicity						
White British	1	1	1	1	1	1
Non-British white	2.0 (1.5 to 2.5)	1.7 (1.4 to 2.2)	1.7 (1.3 to 2.2)	1.7 (1.3 to 2.2)	1.8 (1.4 to 2.3)	1.7 (1.3 to 2.2)
Black Caribbean	6.0 (4.9 to 7.3)	5.3 (4.3 to 6.5)	5.2 (4.3 to 6.4)	5.2 (4.3 to 6.4)	5.4 (4.5 to 6.6)	5.1 (4.2 to 6.3)
Black African	4.1 (3.3 to 5.1)	3.6 (2.9 to 4.5)	3.5 (2.8 to 4.4)	3.5 (2.8 to 4.4)	3.7 (3.0 to 4.6)	3.5 (2.8 to 4.3)
Indian	1.7 (1.2 to 2.5)	1.5 (1.1 to 2.2)	1.5 (1.0 to 2.2)	1.5 (1.0 to 2.1)	1.6 (1.1 to 2.3)	1.6 (1.1 to 2.2)
Pakistani	1.8 (1.2 to 2.5)	1.6 (1.0 to 2.5)	1.6 (1.0 to 2.4)	1.6 (1.0 to 2.4)	1.6 (1.1 to 2.5)	1.8 (1.3 to 2.7)
Bangladeshi	2.1 (1.5 to 2.8)	1.7 (1.2 to 2.3)	1.7 (1.2 to 2.3)	1.6 (1.2 to 2.2)	1.8 (1.3 to 2.5)	1.8 (1.4 to 2.4)
Mixed white and black Caribbean	4.3 (2.8 to 6.7)	3.9 (2.5 to 6.0)	3.9 (2.5 to 6.0)	3.9 (2.5 to 6.0)	4.0 (2.6 to 6.1)	3.9 (2.5 to 6.1)
Mixed, other ethnicities	1.3 (0.8 to 2.3)	1.2 (0.7 to 2.1)	1.2 (0.7 to 2.1)	1.2 (0.7 to 2.1)	1.2 (0.7 to 2.1)	1.2 (0.7 to 2.1)
Other ethnicities	2.2 (1.6 to 3.0)	1.9 (1.4 to 2.7)	1.9 (1.4 to 2.6)	1.9 (1.4 to 2.6)	2.0 (1.4 to 2.7)	1.9 (1.4 to 2.7)
Socioenvironmental variables						
IMD (z-score)	–	1.184 (1.101 to 1.274)	–	–	–	–
Extent of deprivation (%)	–	–	1.008 (1.004 to 1.011)	–	–	–
Income deprivation (%)	–	–	–	1.025 (1.015 to 1.035)	–	–
Employment deprivation (%)	–	–	–	–	1.062 (1.032 to 1.093)	–
Population density (pph)	–	–	–	–	–	1.005 (1.003 to 1.007)
Model-fit diagnostics						
AIC†	2571.8	2552.4	2551.3	2549.6	2556.4	2556.3
Mean Lin's CCC (95% CI)‡	0.75 (0.74 to 0.77)	0.77 (0.75 to 0.78)	0.77 (0.75 to 0.79)	0.77 (0.75 to 0.78)	0.77 (0.75 to 0.78)	0.76 (0.74 to 0.77)
Mean RMSE (SD)§	0.75 (0.11)	0.74 (0.11)	0.74 (0.10)	0.74 (0.10)	0.74 (0.11)	0.76 (0.13)

*All models fitted with age group by sex interaction given a priori evidence for effect modification.[18 45] Likelihood ratio test p values reported between models with and without an interaction term fitted between age group and sex. Specific IRR has not been reported for clarity, but is available on request.
†Lower scores denote improved model fit.
‡Higher scores indicate greater correlation between observed and predicted count of cases in the *prediction sample*. Mean CCC and 95%CI reported following h=20 trials during cross-validation.
§Lower scores indicate lower prediction error. Mean RMSE and SD reported following h=20 repeats of K-fold cross-validation, where K=10.
AIC, Akaike's Information Criterion; CCC, Lin's correlation concordance coefficient; IRR, incidence rate ratio; RMSE, root mean squared error.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

met initial acceptance criteria for EIS in East Anglia. We excluded 50 participants (8.7%) who did not meet clinical criteria for the ICD-10 psychotic disorder. This left an incidence sample of 522 participants from nearly 1.4 m person-years at-risk (37.4/100 000 person-years; 95% CI 34.3 to 40.7). A further 2.3 m person-years at-risk accrued in the same region for people aged 36–64 years over this period. Median levels of multiple, income and employment deprivation in the region did not differ significantly from the remainder of England, although the median population density and extent of deprivation in East Anglia were lower than elsewhere in England (see online supplementary table S1).

External model prediction and validation

The overall observed count of cases, aged 16–35 years, in the *validation sample* (n=522) fell within 95% PIs in four of seven models (models 3–6, table 3). Of these, the observed count (n=522) was closest to the point estimate for model 6 (508.5; 95% PI 449.0, 559.0), fitted with age group, sex, their interaction, ethnic group and LAD population density. The observed count of cases also fell within PIs from this model in five of six EIS in the study region, and 19 of 21 LADs, the most in any model (table 4). This model had the lowest error scores at the EIS (RMSE=11.6) and LAD (RMSE=6.1) levels of any model. Overall, model 6 was ranked highest across all external model-fit diagnostics (table 4). All models outperformed the department of health's uniform figure of 51 per 100 000 person-years (model 7), which generally overestimated cases in the *validation sample* (overall prediction: 715.7 cases; 95% PI 664.0, 769.0).

We reported predicted cases aged 36–64 years from our models (table 4), although we could not test these in the *validation sample*. Model 6 predicted an additional 262.9 cases aged 36–64 years over a 2.5-year period in East Anglia (95% PI 233.0, 297.0).

We inspected the stratum-specific external validity of our best-fitting model (model 6, see online supplementary table S2), which performed accurately for sex-specific predictions, but less well in age-specific and ethnicity-specific strata. Thus, our model tended to underpredict observed cases in people aged 16–19 years, but overpredicted cases observed in people over 25 years old. With respect to ethnicity, model predictions were consistent with observed FEP cases for people of non-British white, black African, Bangladeshi and mixed ethnicities. However, our model tended to underpredict observed rates in the white British group, and overpredicted rates in the black Caribbean, Indian and Pakistani populations.

Extrapolation to England and Wales

We predicted the expected count and incidence of first episode psychosis per annum in each LAD in England and Wales based on model 6, and visualised these data in maps and tables freely available at www.psymaptic.org. Many maps can be visualised (eg, see online supplementary figure S1), including the overall predicted incidence counts and rates for each broad age group at the LAD level, and by sex. We will make PsyMaptic data available by ethnic group when we can improve the validity in ethnic-specific strata. According to our model, the annual number of new FEP cases in England and Wales would be 8745 (95% PI 8558, 8933), of which our model predicted 67.9% (n=5939; 95% PI 5785, 6102) would be seen through EIS. Only 176 (95% PI 151, 203) cases aged 16–64 years were forecast in Wales per annum. Assuming that our prediction model is accurate, it indicated that the Department of Health's current uniform rate of 51/100 000 person-years was higher than the predicted point estimates for rates forecast by our PsyMaptic model in 351 LADs (93%) in England and Wales, but was lower than that predicted by our model in Birmingham and several London boroughs (see online supplementary figure S2, left-hand map). Under a conservative approach, these differences achieved statistical significance in parts of London (where the Department of Health's model underestimated the need as predicted by PsyMaptic), and in some more rural parts of England and Wales (where the Department of Health's model overestimated the need; see online supplementary figure S2, right-hand map).

DISCUSSION

Principal findings

We have developed and tested several epidemiological prediction models to forecast FEP incidence in England and Wales, having taken into account regional differences in the sociodemographic and socioenvironmental profiles of different populations. Inspection of our data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the greatest external predictive validity when compared with the observed FEP caseload ascertained through EIS in our *validation sample*. This model also had good apparent validity across the entire age range (16–64 years). All models outperformed the Department of Health's current gold standard for EIS commissioning,[5] based on a uniform incidence rate. Our data suggested that the original figure used to commission EIS probably overestimated the true incidence of FEP in rural areas, and underestimated rates in urban settings. However, we acknowledge that commissioning decisions will need to be based on several additional factors, including the level of preclinical or non-psychotic psychopathology requiring assessment at initial referral to EIS, and variation in service organisation, remit and delivery.

Limitations and future development

Our prediction models were based on epidemiological data obtained from large, robust population-based FEP studies for people aged 16–64 years.[18 19] The best-fitting model had good apparent validity over this age range,

© 2016 Copyright Clearance Center, Inc. All Rights Reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

Psychosis incidence prediction

Table 3 Observed versus predicted cases in Social Epidemiology of Psychoses in East Anglia study for all clinically relevant psychoses, 16–35 years*

EIS	Observed	Predicted (95% PI) Model 1	Predicted (95% PI) Model 2	Predicted (95% PI) Model 3	Predicted (95% PI) Model 4
Overall total, 16–35 years	522	641.2 (586.0, 696.1)	468.5 (422.0, 518.0)	*474.7 (429.0, 522.0)*	*487.5 (441.0, 535.0)*
CAMEO North	55	84.7 (66.0, 106.0)	*68.5 (52.0, 87.0)*	*67.8 (51.0, 86.0)*	*70.2 (53.0, 90.0)*
CAMEO South	134	163.6 (135.0, 192.0)	105.5 (84.0, 129.0)	*111.7 (89.0, 134.0)*	110.9 (90.0, 132.0)
West Norfolk	26	*29.2 (18.0, 41.0)*	*23.0 (13.0, 35.0)*	*22.0 (12.0, 32.0)*	*23.4 (14.0, 34.0)*
Central Norfolk	120	162.6 (136.0, 191.0)	*122.6 (99.0, 148.0)*	*123.0 (100.0, 149.0)*	*128.3 (104.0, 152.0)*
Great Yarmouth and Waveney	60	*49.1 (34.0, 65.0)*	41.6 (28.0, 55.0)	39.9 (27.0, 53.0)	42.9 (30.0, 57.0)
Suffolk	127	*151.9 (126.0, 178.0)*	*107.4 (85.0, 128.0)*	*110.3 (88.0, 133.0)*	*111.7 (90.0, 136.0)*
Overall total, 36–64 years	–	332.2 (292.0, 373.0)	244.0 (213.0, 276.0)	248.6 (216.0, 280.0)	256.3 (228.0, 291.0)
		Model 5	**Model 6**	**Model 7**	
Overall total, 16–35 years	522	*477.1 (428.0, 523.0)*	*508.5 (459.0, 559.0)*	715.6 (664.0, 769.0)	
CAMEO North	55	*69.1 (52.0, 88.0)*	*64.5 (48.0, 82.0)*	92.1 (74.0, 111.0)	
CAMEO South	134	100.7 (79.0, 123.0)	*131.1 (108.0, 157.0)*	169.0 (144.0, 195.0)	
West Norfolk	26	*24.7 (16.0, 35.0)*	*22.3 (13.0, 33.0)*	*35.8 (25.0, 48.0)*	
Central Norfolk	120	*128.2 (105.0, 153.0)*	*132.5 (108.0, 157.0)*	187.7 (161.0, 215.0)	
Great Yarmouth and Waveney	60	*47.7 (35.0, 63.0)*	38.0 (26.0, 51.0)	*59.1 (44.0, 74.0)*	
Suffolk	127	*106.6 (86.0, 128.0)*	*120.0 (96.0, 143.0)*	172.1 (147.0, 198.0)	
Overall total, 36–64 years	–	249.7 (221.0, 284.0)	262.9 (233.0, 297.0)	1175.4 (1109.0, 1243.0)	

*Numbers in italics denote where the observed count fell within 95% prediction interval (95% PI) for people aged 16–35 years. Observed data for people aged 36–64 years in the *validation sample* were not available.
Model 1: Age group, sex, their interaction and ethnicity.
Model 2: Model 1+IMD.
Model 3: Model 1+extent of deprivation.
Model 4: Model 1+income deprivation.
Model 5: Model 1+employment deprivation.
Model 6: Model 1+population density.
Model 7: Department of health uniform figure for EIS of 15 new cases per 100 000 people/year.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

Table 4 External model validation diagnostics*

Model	Observed case count within SEPEA overall prediction intervals? (rank)	EIS (N=6)		LAD (N=21)		Mean ranking (rank of mean ranking)
		Number correct (rank)	RMSE (rank)	Number correct (rank)	RMSE (rank)	
Model 1	No (5)	3 (6)	26.9 (6)	18 (2)	8.9 (6)	5.0 (6)
Model 2	No (5)	4 (4)	17.0 (4)	18 (2)	6.5 (4)	4.8 (5)
Model 3	Yes (1)	5 (1)	15.1 (2)	17 (5)	6.2 (3)	2.4 (2)
Model 4	Yes (1)	4 (4)	15.1 (2)	17 (5)	6.1 (1)	2.6 (3)
Model 5	Yes (1)	5 (1)	18.0 (5)	18 (2)	6.7 (5)	2.8 (4)
Model 6	Yes (1)	5 (1)	11.6 (1)	19 (1)	6.1 (1)	1.0 (1)
Model 7	No (5)	2 (7)	39.4 (7)	13 (7)	11.7 (7)	6.6 (7)

*For each diagnostic, models are placed in rank order (1=best model, 7=worst model) with ties given the same ranking. The mean ranking and rank provide an estimate of the overall performance of various models.
EIS, early intervention services; LAD, local authority district; RMSE, root mean squared error; SEPEA, Social Epidemiology of Psychoses in East Anglia.

and good external validity over the age range 16–35 years. While 16–35 years covers the majority of adult onset psychosis cases seen in mental health services, we recognise that some EIS teams incept people from 14 years old. We were unable to extrapolate our models to this age range, given the current absence of incidence data for this group in England. Data from Scandinavia suggest that the incidence of such 'early onset' psychoses is absolutely low,[29] although the rate may have increased over the last few decades, probably as a result of movement towards earlier detection. We were also unable to externally validate prediction models for people aged 36–64 years, because comparable observed incidence data were not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models were ascertained from the same two large, well-conducted studies as for data on the younger age group.[18 19 28] Furthermore, published findings from these studies are consistent with the wider epidemiological literature on FEP in England and internationally.[17 21 30] It will be important to validate the predictive capability of our model(s) in this age range, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

Our best-fitting overall model demonstrated excellent external validity for predicting sex-specific FEP cases in our *validation* region (ie, SEPEA). It performed less well across age-specific and ethnic-specific stratum in this region. With respect to age, this discrepancy is most likely to be a function of EIS provision itself, which seeks to intervene as early as possible in the onset of psychosis. The effect of this will reduce median age at onset in comparison to studies conducted prior to the introduction of EIS, such as the ÆSOP and ELFEP studies upon which our models are based. Future versions of PsyMaptic will incorporate empirical data from post-EIS studies to improve age-specific predictions. The validity of our model in some ethnic groups also requires further refinement. Much of the prediction data underlying our models came from urban environments with large proportions of ethnic minority groups. The sociodemographic profile and sociocultural experiences of these groups may be very different to those of their counterparts in other, less urban, parts of England, thus altering psychosis risk in different ethnic groups. In our observed data, a larger proportion of cases were white British than predicted by our model. If ethnicity is a partial proxy for exposure to deleterious socioenvironmental experiences, such as the combined effect of social inequality, fragmentation, deprivation and population density,[31] then simultaneously incorporating such factors into our models may improve their predictive validity by ethnicity. Alternatively, risk by ethnic group may be conditional upon (ie, interact with) environmental factors in urban areas (as with the ethnic density effect[32 33]), but whether such interactions exist in less urban regions is not known. Forthcoming SEPEA and PsyMaptic data will explore such possibilities.

All prediction models had reasonable apparent validity, although our proposed model performed slightly worse (most noticeably for AIC) than models which included deprivation (ie, models 2–4) instead of population density. Our decision to use model 6 as our proposed candidate for the prediction tool was supported by the fact that it produced the most accurate external forecasts of any model, despite considerable socioenvironmental differences between regions in our *prediction* and *validation* samples. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards, or to other parts of the UK, because appropriate denominator data were not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK, scheduled for release in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. We will then be able to develop models to explore cross-level interactions, such as the association between individual ethnicity and neighbourhood-level ethnic density. Small

© 2016 Copyright Clearance Center, Inc. All Rights Reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16–35 years. EIS were the only mental health service for people aged 14–35 years experiencing a first episode of psychosis in East Anglia, minimising the potential for underascertainment in the population at-risk when derived from careful epidemiological design.[13] We are confident that our *validation sample* also contained few false positive cases for any clinically relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS, or who did not meet clinical diagnosis for psychotic disorder in the first 6 months following EIS acceptance. It is important to recognise that while our prediction models are based on diagnosed clinically relevant psychotic disorders, service commissioning will also need to account for additional preclinical or non-psychotic psychiatric morbidity presenting to EIS, particularly in services which operate early detection models or implement 'watch-and-wait' briefs. The SEPEA data used to validate our models do not predict (1) the number of 'false positive' subjects who may require psychiatric triage and assessment, even though they are not accepted by EIS or (2) the number of 'true positive' subjects accepted by services, but who did not meet epidemiological criteria for inclusion in the *validation sample* of the SEPEA study (ie those living outside the catchment area at first contact, or those transferred from other services); these people will consume varying degrees of service resources which need to be considered in service planning.

We also note that pathways to care may affect the level of incidence observed in EIS, since many filters are likely to operate before subjects come to the attention of EIS. These will include local level service organisation and the relationship between Community Mental Health Teams, Child and Adolescent Mental Health and EIS. Furthermore, acceptance criteria for entry to EIS vary, which will have a downstream effect on the number of new cases of clinically relevant psychoses received in each team. Future versions of PsyMaptic will include forecasts for specific psychotic disorders, as standardised research-based diagnoses (using OPCRIT[34]) are currently being collected in the ongoing SEPEA study. Acceptance rates to EIS may also be influenced by local community awareness of such services. While our prediction models outperformed the current gold standard for EIS commissioning in England when restricted to clinically relevant caseloads, we recommend that our models are best interpreted as forecasts of the expected burden of first episode psychosis in given populations, not the total burden of resource consumption through EIS, given these issues.

We estimated PIs from first principles (DJ) since their derivation is an area of statistical development.[35] We used a bootstrap-like methodology to produce 95% PI accounting for natural variation in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which we assumed to be the true coefficients of risk in the population. Our approach therefore naturally led to slightly artificially narrow 95% PIs. This was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts, because we wished to apply stringent criteria. Ideally, 95% PIs should take into account both these sources of variation, although we note that parameter uncertainty is usually small compared with the natural variation of the quantities of interest. The addition of more empirical data in the *prediction sample* would not lead to narrower 95% PIs, though it would tend to move the point estimate of risk for each coefficient closer to the true value in the population. We do not believe we have misestimated the point estimates of risk across major sociodemographic groups, since our results accord with the wider literature.[17 21 22] We sought independent confirmation that our development of 95% PI was correct (personal communication with Professor Ian White, MRC Biostatistics Unit). We recommend that all prediction point estimates from our PsyMaptic model are considered with their 95% PIs, which provide information about the natural variance in expected rates in the population.

Meaning of the findings

If commissioners are to meet the Department of Health's vision to orientate health services around local need,[1 2 5] differences in the demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data are combined with accurate population at-risk estimates, this can be realised. As such, our modelling approach could have utility in many other settings and for many disorders. Our translational approach demonstrated good validity to predict the expected incidence of first episode psychosis, particularly through EIS, where 76% and 63% of all male and female adult-onset FEP cases, respectively, will typically present.[18] Since their inception in 2002, EIS in England and Wales have reported both lower[11] and higher[10] caseloads than they were originally envisioned to manage,[5] with shortfalls or excesses in anticipated demand for services aligned to the degree of urbanisation in the underlying catchment area. Others have noted that EIS provision in rural areas may be difficult to implement effectively,[14 15] and while the MH-PIG acknowledged that "…(a)n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (ref. 5, p. 55), no further elaboration on how to achieve this was provided. We

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

believe PsyMaptic provides a possible tool to overcome this challenge, improving the description and prediction of local population need beyond the MH-PIG and including individual-level and neighbourhood-level indicators of local need.[17] From an aetiological perspective, we acknowledge that variables such as ethnicity or population density are likely to be markers for a suite of more complex, interactive social, genetic and environmental determinants of psychosis.[36]

Our models are not the first to be used to forecast mental illness needs in England and Wales,[37] though we believe this is the first attempt to forecast incidence rather than prevalence in the community. We recommend that our prediction methodology is used in conjunction with the wide range of public health observatory data available,[38] as well as the caveats presented above. PsyMaptic has been included with other indicators in the Joint Commissioning Panel for Mental Health's forthcoming guidance for commissioning of public mental health services.[39] Ongoing monitoring and audit of EIS will be vital to ensure that services meet the fidelity criteria upon which they were originally commissioned,[11 40] including ensuring that service capacity matches local need as closely as possible. As part of this process, we will need to externally validate our models in a wider range of settings, refining them based on empirical observation.

We note that advocacy expressed for EIS by healthcare professionals in England and Wales broadly correlates with demand for services as predicted by PsyMaptic.[41] Though by no means universal, proponents of EIS tend to be located in major conurbations—such as London,[42] Birmingham[43] or Manchester[7 44]—where the demand for EIS will be highest, while those who suggest EIS resources could be used more effectively through other types of mental health service provision tend to work in more rural communities,[15 41] where but a handful of young people would be expected to come to the attention of services each year. It is possible that both sides are correct and that more resources are required to help with the tide of psychotic illness in inner cities. Resources might be used more effectively in other ways, elsewhere, so long as the needs of the small number of young people who suffer an FEP each year are met; a dedicated specialist EIS may not be the most effective approach when anticipated demand will be very low.

Given the significant downstream economic savings associated with spending on EIS as estimated in an urban setting,[8] PsyMaptic could be used to highlight regions where sufficient investment to appropriate mental health services would lead to the greatest economic gains in terms of mental healthcare expenditure (assuming sustained intervention also leads to improved social and clinical benefit for patients[6 7]). PsyMaptic can also be used to highlight regional variation in demand according to age and sex and, in future versions, by ethnicity. This will allow service planners to tailor provision around the sociocultural characteristics of their local populations. Our prediction tool for first episode psychosis, which translates robust empirical epidemiological data on psychosis risk to the population structure of different regions, offers a methodology for improving the allocation of finite mental health resources based on local need.

Author affiliations
[1]Department of Psychiatry, University of Cambridge, Herchel Smith Building for Brain & Mind Sciences, Cambridge, UK
[2]MRC Biostatistics Unit, Institute of Public Health, University of Cambridge, Forvie Site, Robinson Way, Cambridge, UK
[3]CAMEO, Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK
[4]Norfolk and Suffolk Partnership Trust, Hellesdon Hospital, Norwich, UK
[5]Suffolk Early Intervention Psychosis Service, Norfolk and Suffolk Partnership Trust, Stowmarket, Suffolk, UK
[6]Forensic Psychiatry Research Unit, Queen Mary's University London, St. Bartholomew's Hospital, London, UK
[7]Department of Psychosis Studies, Institute of Psychiatry, London, UK
[8]NIHR Collaboration for Leadership in Applied Health Research & Care, Cambridge, UK

Acknowledgements The authors are grateful to the clinical services and staff participating in the SEPEA study, and the MHRN for their support. We are grateful to Professor Ian White of the MRC Biostatistics Unit (University of Cambridge) for his guidance on developing our prediction interval methodology for negative binomial regression.

Contributors JBK was responsible for the concept, design, analysis, data extrapolation, interpretation of the data, as well as for drafting the report and developing the content for the websites www.psymaptic.org, www.psymaptic.com and www.psymaptic.co.uk. He was also the chief investigator of the SEPEA study, where the *validation sample* data were obtained. JBK gave final approval of this version of the manuscript to be published. DJ was responsible for developing and initially implementing the statistical approach with regard to prediction intervals from count-based regression. He also contributed to drafting and editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published. JP is the principal collaborator on the SEPEA study in the CAMEO early intervention in psychosis services. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published. DF is the coprincipal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published. FW is the coprincipal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published. JC is the chief investigator of the ELFEP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published. RMM is the cochief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published. PBJ is the cochief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He contributed to the development of the prediction methodology and edited the final version of this manuscript. He gave final approval of this version of the manuscript to be published. JBK is the guarantor.

Funding Wellcome Trust (grant number WT085540) and NIHR (grant RP-PG-0606-1335).

Competing interests All authors declare that JBK has support from the Wellcome Trust for the submitted work (grant number WT085540) and PBJ has support from the NIHR (grant RP-PG-0606-1335).

© 2016 Copyright Clearance Center, Inc. All Rights Reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Downloaded from http://bmjopen.bmj.com/ on January 9, 2015 - Published by group.bmj.com

Psychosis incidence prediction

Ethics approval Ethics approval to conduct the original ÆSOP and East London First Episode Psychosis studies was granted from local research ethics committees in their respective centres prior to the original date of onset of the study. We were granted ethical approval to conduct the work related to the present manuscript, including the use of data from the SEPEA study, from the Cambridgeshire 3 REC (09/H0306/39).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data are available at our prediction website, PsyMaptic: http://www.psymaptic.org. We have made a large array of prediction data freely available to interested users, who can visualise prediction data in maps and tables for a range of psychotic disorder predictions by major sociodemographic subgroups and by LAD. Future versions of PsyMaptic will release data for other regions and at other geographical levels. Users can also download LAD-specific and national summaries of prediction data from our models in tabular form. Finally, additional explanatory material about how to use the data and the PsyMaptic website is also available at http://www.psymaptic.org. Bespoke data not provided freely on our website may be requested from the authors at the cost of data extraction. The empirical data underlying the prediction models (ÆSOP and ELFEP) or the validation sample (SEPEA) are not freely available as the studies are ongoing, but papers detailing the main findings from these studies have previously been published elsewhere.

REFERENCES

1. Department of Health. *Guidance on joint strategic needs assessment*. London: Department of Health, 2007.
2. Department of Health. *No health without mental health: a cross-government mental health outcomes strategy for people of all ages*. London: Department of Health, 2011.
3. World Health Organisation. *Global burden of disease report*. Geneva: WHO, 2008.
4. McCrone P, Park A-L, Knapp M. *Early intervention for psychosis*. London: Department of Health, 2011.
5. Department of Health. *Mental health policy implementation guide*. London: National Health Service, 2001.
6. Bertelsen M, Jeppesen P, Petersen L, *et al*. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Arch Gen Psychiatry* 2008;65:762–71.
7. Marshall M, Rathbone J. Early intervention for psychosis. *Schizophr Bull* 2011;37:1111–14.
8. Mihalopoulos C, Harris M, Henry L, *et al*. Is Early intervention in psychosis cost-effective over the long term? *Schizophr Bull* 2009;35:909–18.
9. Valmaggia LR, McCrone P, Knapp M, *et al*. Economic impact of early intervention in people at high risk of psychosis. *Psychol Med* 2009;39:1617–26.
10. Mahmmood MA, Fisher H. The incidence of first episode psychosis in inner London: findings from the Lambeth early onset (LEO) service. *Schizophr Res* 2006;86:0548.
11. Tiffin PA, Glover G. From commitment to reality: early intervention in psychosis services in England. *Early Interv Psychiatry* 2007;1:104–7.
12. Cheng F, Kirkbride JB, Lennox BR, *et al*. Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting. *Psychol Med* 2011;41:949–58.
13. Kirkbride JB, Stubbins C, Jones PB. Psychosis incidence through the prism of early intervention services. *Br J Psychiatry* 2012;200:156–7.
14. Craig T. A step too soon or a step too far? Early intervention in psychosis. *J Mental Health* 2003;12:335–9.
15. Kelly M, O'Meara Howard A, Smith J. Early intervention in psychosis: a rural perspective. *J Psychiatr Mental Health Nurs* 2007;14:203–8.
16. McGrath JJ. The surprisingly rich contours of schizophrenia epidemiology. *Arch Gen Psychiatry* 2007;64:14–16.
17. Kirkbride JB, Errazuriz A, Croudace TJ, *et al*. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. *PLoS ONE* 2012;7:e31660.
18. Kirkbride JB, Fearon P, Morgan C, *et al*. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center æsop study. *Arch Gen Psychiatry* 2006;63:250–8.
19. Kirkbride JB, Barker D, Cowden F, *et al*. Psychoses, ethnicity and socio-economic status. *Br J Psychiatry* 2008;193:18–24.
20. Coid JW, Kirkbride JB, Barker D, *et al*. Raised incidence rates of all psychoses among migrant groups: findings from the East London first episode psychosis study. *Arch Gen Psych* 2008;65:1250–8.
21. McGrath J, Saha S, Welham J, *et al*. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med* 2004;2:1–22.
22. Cantor-Graae E, Selten J-P. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry* 2005;162:12–24.
23. Noble M, Wright G, Dibben C, *et al*. *Indices of deprivation 2004*. London: ODPM, 2004.
24. Office for National Statistics. Population Estimates by Ethnic Group (experimental), Mid-2009. Office for National Statistics.. http://www.ons.gov.uk/ons/rel/peeg/population-estimates-by-ethnic-group–experimental-/current-estimates/index.html (accessed 29 January 2013).
25. Department for Communities and Local Government. *English Indices of deprivation 2010*. Newport: Department for Communities and Local Government, Crown Copyright, 2011.
26. Borra S, Ciaccio AD. Measuring the prediction error. A comparison of cross-validation, bootstrap and covariance penalty methods. *Comput Stat Data Anal* 2010;54:2976–89.
27. Statplanet Plus (computer program). Version 3.0. Melbourne, Australia: StatSilk, 2010.
28. Fearon P, Kirkbride JB, Morgan C, *et al*. Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. *Psychol Med* 2006;36:1541–50.
29. Okkels N, Vernal DL, Jensen SOW, *et al*. Changes in the diagnosed incidence of early onset schizophrenia over four decades. *Acta Psychiatrica Scandinavica* 2012;127:62–8.
30. Jablensky A, Kirkbride JB, Jones PB. Schizophrenia: the epidemiological horizon. In: Weinberger DR, Harrison PJ, eds. *Schizophrenia*. 3rd edn. Chichester: Wiley-Blackwell, 2011:185–225.
31. Kirkbride JB, Jones PB, Ullrich S, *et al*. Social deprivation, inequality, and the neighborhood-level incidence of psychotic syndromes in East London. *Schizophr Bull* 2012: doi:10.1093/schbul/sbs151.
32. Kirkbride J, Boydell J, Ploubidis G, *et al*. Testing the association between the incidence of schizophrenia and social capital in an urban area. *Psychol Med* 2008;38:1083–94.
33. Veling W, Susser E, Van Os J, *et al*. Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. *Am J Psychiatry* 2008;165:66–73.
34. Craddock M, Asherson P, Owen MJ, *et al*. Concurrent validity of the OPCRIT diagnostic system. Comparison of OPCRIT diagnoses with consensus best-estimate lifetime diagnoses. *Br J Psychiatry* 1996;169:58–63.
35. Krishnamoorthy K, Peng J. Improved closed-form prediction intervals for binomial and Poisson distributions. *J Stat Plann Inference* 2011;141:1709–18.
36. Kirkbride JB, Jones PB. The prevention of schizophrenia—what can we learn from eco-epidemiology? *Schizophr Bull* 2011;37:262–71.
37. Glover G, Arts G, Wooff D. A needs index for mental health care in England based on updatable data. *Soc Psychiatry Psychiatr Epidemiol* 2004;39:730–8.
38. North East Public Health Observatory. Community Mental Health Profiles. North East Public Health Observatory. http://www.nepho.org.uk/cmhp/ (accessed 29 January 2013)
39. Joint Commissioning Panel for Mental Health. *Guidance for the commissioning of public mental health services*. London: Royal College of Psychiatry, 2012.
40. Pinfold V, Smith J, Shiers D. Audit of early intervention in psychosis service development in England in 2005. *Psychiatr Bull* 2007;31:7–10.
41. Pelosi AJ, Birchwood M. Is early intervention for psychosis a waste of valuable resources? *Br J Psychiatry* 2003;182:196–8.
42. Power P, McGuire P, Iacoponi E, *et al*. Lambeth Early Onset (LEO) and Outreach & Support in South London (OASIS) service. *Early Intervention Psychiatry* 2007;1:97–103.
43. Lester H, Birchwood M, Bryan S, *et al*. Development and implementation of early intervention services for young people with psychosis: case study. *Br J Psychiatry* 2009;194:446–50.
44. Marshall M, Lockwood A, Lewis S, *et al*. Essential elements of an early intervention service for psychosis: the opinions of expert clinicians. *BMC Psychiatry* 2004;4:17.
45. Hafner H, Riecher A, Maurer K, *et al*. How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. *Psychol Med* 1989;19:903–18.

Appendix 4 Social and spatial heterogeneity in psychosis proneness in a multilevel case–prodrome–control study

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2014: 1–10
All rights reserved
DOI: 10.1111/acps.12384

© 2014 The Authors. Acta Psychiatrica Scandinavica Published by John Wiley & Sons Ltd.
ACTA PSYCHIATRICA SCANDINAVICA

Social and spatial heterogeneity in psychosis proneness in a multilevel case–prodrome–control study

Kirkbride JB, Stochl J, Zimbrón J, Crane CM, Metastasio A, Aguilar E, Webster R, Theegala S, Kabacs N, Jones PB, Perez J. Social and spatial heterogeneity in psychosis proneness in a multilevel case–prodrome–control study.

Objective: To test whether spatial and social neighbourhood patterning of people at ultra-high risk (UHR) of psychosis differs from first-episode psychosis (FEP) participants or controls and to determine whether exposure to different social environments is evident before disorder onset.
Method: We tested differences in the spatial distributions of representative samples of FEP, UHR and control participants and fitted two-level multinomial logistic regression models, adjusted for individual-level covariates, to examine group differences in neighbourhood-level characteristics.
Results: The spatial distribution of controls (n = 41) differed from UHR (n = 48; P = 0.04) and FEP participants (n = 159; P = 0.01), whose distribution was similar (P = 0.17). Risk in FEP and UHR groups was associated with the same neighbourhood-level exposures: proportion of single-parent households [FEP adjusted odds ratio (aOR): 1.56 95% CI: 1.00–2.45; UHR aOR: 1.59; 95% CI: 0.99–2.57], ethnic diversity (FEP aOR: 1.27; 95% CI: 1.02–1.58; UHR aOR: 1.28; 95% CI: 1.00–1.63) and multiple deprivation (FEP aOR: 0.88; 95% CI: 0.78–1.00; UHR aOR: 0.86; 95% CI: 0.76–0.99).
Conclusion: Similar neighbourhood-level exposures predicted UHR and FEP risk, whose residential patterning was closer to each other's than controls. Adverse social environments are associated with psychosis before FEP onset.

J. B. Kirkbride[1,2], J. Stochl[2,*], J. Zimbrón[2,3], C. M. Crane[2,3], A. Metastasio[3,†], E. Aguilar[3,‡], R. Webster[3], S. Theegala[3], N. Kabacs[3], P. B. Jones[2], J. Perez[2,3]

[1]Division of Psychiatry, UCL, London, UK, [2]Department of Psychiatry, University of Cambridge, Cambridge, UK, [3]Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK, *Present address: Department of Health Sciences, University of York, York, UK, †Present address: Norfolk & Suffolk Foundation Trust, Ipswich, UK and ‡Present address: Department of Mental Health, Parc Tauli Sabadell University Hospital, Barcelona, Spain

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Key words: psychotic disorders; social environment; epidemiology; prodromal symptoms; population spatial distribution

James Kirkbride, Sir Henry Dale Fellow, Division of Psychiatry, UCL, 67-73 Riding House Street, London W1W 7EJ, UK. E-mail: j.kirkbride@ucl.ac.uk

Accepted for publication December 1, 2014

Significant outcomes

- The spatial distribution of controls differed from ultra-high risk (UHR) and first-episode psychosis (FEP) participants, who did not differ from each other.
- The same neighbourhood-level social environmental exposures predicted elevated risk in both the UHR and FEP groups relative to controls, to a similar extent.
- The spatial patterning of FEP is unlikely to be solely due to social drift following the onset of disorder.

Limitations

- This multilevel study used cross-sectional data to compare social and spatial differences in the three groups in a defined catchment area; we did not have longitudinal data on transition to psychosis in UHR participants.
- Controls were broadly similar to the population at risk in sociodemographic terms but came from more densely populated neighbourhoods, making odds ratios conservative.
- We had a relatively small sample of controls and UHR participants in this study.

© 2014 The Authors. Acta Psychiatrica Scandinavica Published by John Wiley & Sons Ltd.

Kirkbride et al.

Introduction

The incidence of schizophrenia and other non-affective psychotic disorders is elevated in more densely populated urban areas (1–3), often characterised by greater social and economic disadvantage (4–10). Evidence that urban birth and childhood upbringing increase schizophrenia risk in adulthood is consistent with an aetiological role for environment factors (8–10), although downward social drift of people in their first episode of psychosis (FEP) into lower socio-economic positions or communities, as a consequence of disorder, has not been entirely refuted. As both causal and consequential factors may explain a degree of the social and spatial patterning of schizophrenia, further investigation of their respective roles is putatively important for both prevention and management of clinical services for people with FEP. Here, careful examination of the social epidemiology of people who meet ultra-high risk (UHR) criteria for psychosis (due to familial risk and/or early prodromal criteria) may be informative, as this group do not meet diagnostic threshold for FEP. At the individual level, greater psychosocial stress (11), lower social support (11), childhood trauma (12, 13) and receipt of welfare benefits (14) are reported to predict UHR status, in line with similar risk factors for psychotic disorders. Less research has focussed the role of the wider social environment in relation to UHR status. One study observed that urban living was associated with greater risk of transition in a UHR sample (14), although another did not (15). No study has, however, compared the spatial distribution and detailed characteristics of the social environment amongst people with FEP, UHR and population-based control subjects in a single epidemiological sample, which forms the focus of the present investigation.

Aims of the study

We hypothesised that people with first-episode psychosis would have a different social and spatial distribution to controls, towards more socially disadvantaged communities, and that this would be stronger for non-affective psychotic disorders in line with previous literature; affective psychoses do not appear to vary by urbanicity. We also hypothesised that the sociospatial distribution of the ultra-high risk group would differ from controls, in similar ways to people with first-episode psychosis, which together would support the possibility that associations between psychotic disorders and the social environment cannot solely be attributable to social drift following onset.

Material and methods

Study design and setting

We used a cross-sectional study design to identify all incidence cases of FEP, a sample of people meeting UHR criteria for subthreshold psychosis and population-based controls in the defined catchment area of the Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) in the East of England, UK, over a 20-month period.

Participants with first-episode psychosis

All people with suspected FEP referred to the CAMEO early intervention in psychosis service (EIS) were potentially eligible for inclusion. Participants were identified via the Social Epidemiology of Psychoses in East Anglia (SEPEA) study (16), a larger study of all FEP contacts presenting to six EIS in East Anglia, aged 16–35 years, over 3·5 years. To ensure consistency with the UHR group, we restricted the sample to people first referred between 1 February 2010 and 30 September 2012. Inclusion criteria were as follows:

i) Presence of psychotic symptoms at acceptance into EIS care.
ii) No previous referral to mental health services for psychotic symptoms or treatment with antipsychotic medication.
iii) Aged 18–35 years (to correspond with control age range, see below).
iv) Resident within the catchment area at referral.
v) Absence of acute intoxication due to substance abuse or withdrawal, an organic basis to presentation or severe learning difficulty (defined by a Weschler Adult Intelligence Scale IQ score < 70).

Six months after EIS acceptance, or discharge from the service (whichever was sooner), a research-based diagnosis was obtained using the operationalised criteria checklist (OPCRIT) (17), a reliable (17, 18) and validated (19) 90 symptom-item assessment for establishing psychiatric diagnoses based on case note review. Participants who met criteria for International Classification of Diseases, Tenth Revision (ICD-10) F20–33 psychotic disorders were included, with non-affective (F20–29) and affective psychotic disorder (F30–33) also treated as separate subgroups for analyses. Raters first received OPCRIT training, rating the same set of 12 anonymous case vignettes (not participants in the present study) to establish reliability; formal inter-rater reliability statistics could not be estimated on 12 vignettes, but percentage agreement ranged from 83% to 100%, based on a comparison

of ICD-10 non-affective psychosis (F20–29), affective psychosis (F30–33) or not psychotic (data available from authors).

Participants at ultra-high risk for psychosis

People meeting UHR criteria for psychosis were identified as part of the PAATh study (20), which ran in parallel to the SEPEA study in CAMEO. All people referred to CAMEO were screened according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) (21), a clinical instrument with good reliability and valid criteria for the identification of UHR individuals. Inclusion criteria were identical to those for people with FEP, except that they met CAARMS criteria for either.

i) Attenuated psychosis (subthreshold symptom intensity or frequency), or
ii) Brief Limited Intermittent Psychotic Symptoms (threshold symptoms lasting no longer than one continuous week in the last year and having not persisted for over five years), or
iii) A family history of psychosis in a first-degree relative or schizotypal personality disorder in the proband, plus a 30% drop in Global Assessment of Functioning (GAF) score from premorbid level, sustained for a month, within the past 12 months, or GAF score of 50% or less for the past 12 months.

Control participants

Controls, aged 18–35 years old, without psychosis, were identified from an embedded project within the SEPEA study, the European Union Gene-Environment Interaction (EU-GEI) study. This is an ongoing international, multi-centre case–sibling–control study of gene–environment interactions in schizophrenia and other psychoses in people aged 18–64 years (22). Controls were identified via multistage, stratified random sampling to ensure representativeness to the population at risk. First, a sampling frame of all general practices (GPs) (N = 103) within the CPFT catchment area was established, from which we randomly invited 20 practices to participate. Due to refusal (N = 14), we resampled 20 further practices, without replacement, until ten practices had been enrolled. Second, GP patient lists were screened (by the practice manager) to exclude people who did not meet inclusion criteria (as above, but not meeting FEP or UHR criteria). GPs also retained the right to remove any patients deemed inappropriate for contact (such as recently bereaved individuals), which was minimal in practice. From each patient list, we randomly invited 150 participants to take part in the EU-GEI study, contacted by letter and follow-up phone calls. Participants who responded positively were recruited for full EU-GEI assessment until an *a priori* target (n = 105) had been achieved.

Individual sociodemographic variables

We collected baseline sociodemographic data on participants at first contact, including age, sex, ethnic group, main or last occupation and residential postcode. Self-ascribed ethnicity to one of 18 major ethnic groups, as per the 2011 Census of Great Britain (23), was collapsed for analysis into a six-category variable (white British, white other, black, Asian, mixed ethnicities, other) and a binary variable [white British, all black and minority ethnic (BME) groups]. Main occupation was coded to the National Statistics Socioeconomic Classification (NS-SEC) 6-category socioeconomic variable, adhering to strict decision rules (24): professional and managerial occupations, intermediate and self-employed, semi-routine and routine, students, long-run unemployed, otherwise unclassifiable. Highest main (or if not available, current, or last) parental occupation (fathers' or mothers') was coded similarly.

Neighbourhood-level socioenvironmental exposures

We geocoded each participant's residential postcode to their corresponding latitude/longitude coordinates (British National Grid) to (i) examine differences in the spatial distribution of the three groups, and (ii) assign participants to their neighbourhood of residence, delimited here by 2011 census wards [N = 150 wards, median population: 4984; interquartile range (IQR): 2761–7430]. For each ward (henceforth the 'neighbourhood'), we measured *a priori* socioenvironmental exposures, estimated from the 2011 census (see Table 1 for full details): neighbourhood-level population density (people per hectare), proportion of households deprived on at least two of four 2011 census deprivation domains (25), inequality in multiple deprivation between output areas (OA) (median population: 311; IQR: 267–353) nested within each neighbourhood (7), proportion of single-person households, proportion of single-parent households, proportion of people aged 18–35 years old (as a marker of social isolation from other young people), own-group ethnic density (estimated for the six ethnic groups), own-group ethnic segregation (the extent to which each ethnic group was concentrated at OA-level within each neighbour-

© 2014 The Authors. Acta Psychiatrica Scandinavica Published by John Wiley & Sons Ltd.

Table 1. Overview of included neighbourhood-level (electoral ward) socioenvironmental exposure variables*

Variable	Source(s)	Description
Population density	Table QS103EW 2011 Census	People per hectare, estimated from usual resident population size divided by ward area
% multiple deprivation	Table QS119EW 2011 Census	Proportion of households classified as meeting criteria for deprivation on at least two of four Census domains (employment, education, health and housing quality). See (25) for full details of Census methodology
% inequality in multiple deprivation	Table QS119EW 2011 Census	Estimate of disparity in *% multiple deprivation* at smaller geographical level (Output Area) within each electoral ward. Calculated using Gini coefficient and expressed as a proportion (0 = no inequality, 100 = perfect inequality)
% single-person households	Table KS105EW 2011 Census	Proportion of single-person households as a total of all households per ward
% single-parent households	Table KS105EW 2011 Census	Proportion of single-parent households with dependent children as a total of all households per ward
% people aged 18–35 years	Table QS103EW 2011 Census	Proportion of the total population per ward aged 18–35 years old as a marker of social isolation amongst young people
% own-group ethnic density	Table DC2101EW Census 2011	Proportion of total population per ward belonging to each given ethnic group
% own-group ethnic segregation	Table DC2101EW Census 2011	Extent to which each ethnic group was concentrated or dispersed across each ward [at output areas (OA)-level], relative to all other groups. Estimated using Index of Dissimilarity (7). (0 = total integration, 100 = total segregation)
% ethnic diversity	Table KS201EW Census 2011	Measure borrowed from ecology to estimate diversity (26), defined by the reciprocal diversity index, which here estimates the total number ethnic groups in a neighbourhood (N_{max} = 18), weighted by their population size; it may range from 1 to N_{max} and is rescaled as a proportion (0 = maximum ethnic homogeneity, 100 = maximum ethnic diversity)

*Variables estimated from the Office for National Statistic's 2011 Census of Great Britain (23).

hood) (6) and ethnic diversity [a measure borrowed from ecology to estimate diversity (26)].

Statistical methods

Prior to our main statistical analysis, we assessed whether our final sample of control participants was representative of the wider population at risk by comparing them to excluded participants and the population at risk in the catchment area estimated from the 2011 Census of Great Britain (23) on a range of individual and neighbourhood-level exposures. Chi-squared tests and Fisher's exact tests were used to compare categorical variables (sex, ethnicity, socioeconomic status); Mann–Whitney *U*-tests were used to test median differences in continuous variables (age, neighbourhood variables). Differences in individual-level exposures between FEP, UHR and control participants were assessed similarly.

We next inspected whether the spatial distribution of people with FEP, the UHR group and controls differed at first contact using a two-dimensional *M*-test (27, 28). This assesses whether the distribution of interpoint distances between all observations from two participant groups (i.e. FEP vs. controls, FEP vs. UHR participants, etc.) differs in a two-dimensional space (i.e. latitude/longitude); the null hypothesis is that the two groups come from the same spatial distribution. Next, we inspected whether any neighbourhood-level socioenvironmental exposures might be associated with such differences by fitting two-level (individuals nested in neighbourhoods), multinomial logistic regression models. Multinomial models allow for the simultaneous estimation of risk (i.e. odds) in the UHR and FEP group relative to controls. By extending these models to a multilevel framework, we can estimate unmeasured variation in psychosis proneness attributable to neighbourhood effects, via inclusion of a latent random effect. We had no reason to assume the neighbourhood would have different (random) effects on UHR or FEP risk and so fitted a single random intercept which could vary between neighbourhoods, but was constrained to have the same effect across groups.

A null model (without covariates or 'fixed' effects) was first fitted to quantify variation in psychosis proneness attributable to neighbourhood random effects. Next, we entered neighbourhood-level fixed effects one-by-one into univariable models to examine their association with psychosis proneness (control vs. UHR vs. FEP). Model fit was assessed via Akaike's Information Criterion (AIC), where lower scores indicated better fit. We then employed a backward-fitting modelling strategy to identify our best-fitting model, having included all individual variables as potential *a priori* confounders. All neighbourhood-level variables were tested sequentially (in order of poorest AIC from univariable analyses) for removal from the model, assessed via a permissive likelihood ratio test criteria of $P < 0.10$. To examine whether non-affective and affective psychotic disorders differed

with respect to the environment, we refitted our final model with these disorders as separate multinomial outcomes. We reported odds ratios (OR) and 95% confidence intervals (95% CI). Modelling was conducted in STATA (version 13, StataCorp, College Station, TX, USA), with two-level multinomial logistic regressions fitted via generalised structural equation models (*gsem*).

Ethics committee approval

The SEPEA, PAATh and EU-GEI studies received full ethical approval from the Cambridgeshire East Research Ethics Committee.

Results

Sample representativeness

One-hundred and eighty-nine people, aged 18–35 years, with potential FEP were accepted by CAMEO over the study period, of whom 22 were excluded because of the absence of an OPCRIT-confirmed ICD-10 diagnosis. A further eight clients of no fixed abode were also excluded, leaving 159 people with FEP in the present analyses, of which 131 (82.3%) received an ICD-10 diagnosis of non-affective psychosis. Excluded FEP participants did not differ by median age (Mann–Whitney *U*-test $P = 0.21$), sex (χ^2-test $P = 0.74$), ethnic status (white British vs. BME: χ^2-test $P = 0.96$), marital status (χ^2-test $P = 0.69$), or highest participant (Fisher's Exact test $P = 0.94$) or parental (Fisher's Exact test $P = 0.30$) socioeconomic status. Forty-nine people met UHR criteria for psychosis (all CAARMS criteria 1), of whom one participant living outside of the catchment area at first contact, was excluded. Forty-one EU-GEI controls, aged 18–35 years, were included in this analysis.

Controls were representative of the population at risk from the 2011 census in terms of available sociodemographic data on age group (Fisher' Exact test $P = 0.76$), sex (χ^2-test $P = 0.54$), white British vs. BME ethnicity (χ^2-test $P = 0.83$) and socioeconomic status (Fisher's Exact test $P = 0.34$). Data on marital status and parental socioeconomic status could not be compared as these were not available from the 2011 Census for the population at risk aged 18–35 years. Control neighbourhoods were representative of the wider CPFT catchment area in terms of median deprivation (20.2% vs. 20.7%; Mann–Whitney *U*-test $P = 0.15$), inequality (23.3% vs. 20.5%; Mann–Whitney *U*-test $P = 0.72$), single-parent households (4.8% vs. 4.7%; Mann–Whitney *U*-test $P = 0.25$) and ethnic segregation (18.2% vs. 19.8% Mann–Whitney *U*-test $P = 0.90$), but were more densely populated (11 people per hectare vs. 2.1; Mann–Whitney *U*-test $P = 0.06$), ethnically diverse (2.7% vs. 0.7%; Mann–Whitney *U*-test $P = 0.002$) and had higher proportions of people aged 18–35 years (24.5% vs. 16.8%; Mann–Whitney *U*-test $P = 0.004$) and single-person households (28.7% vs. 26.3%; Mann–Whitney *U*-test $P = 0.03$).

Participant characteristics

Controls were significantly older than FEP ($P = 0.02$) or UHR participants ($P < 0.001$) (Table 2). We observed a trend for greater proportions of men with increased psychosis proneness ($P = 0.06$), while controls held higher socioeconomic occupations than their UHR or FEP counterparts ($P = 0.003$). Differences in highest parental socioeconomic occupations were also apparent ($P = 0.04$), with parents of UHR participants somewhat over-represented in professional and managerial occupations.

Spatial distribution of participants at first contact

The spatial distribution of controls differed from both the FEP ($P = 0.01$) and UHR groups (*M*-test $P = 0.04$) (Fig. 1a,b). There was no evidence that the spatial distribution of the FEP group differed from the UHR group ($P = 0.17$; Fig. 1c). These patterns held when the analyses were restricted to people with non-affective FEP ($n = 131$; vs. controls: $P = 0.01$; vs. UHR: $P = 0.22$) and affective psychoses ($n = 28$; vs. controls: $P = 0.01$; vs. UHR: $P = 0.62$), whose spatial distributions also differed significantly from each other ($P = 0.01$; Fig. 1d).

Multilevel multinomial regression

A null multilevel model provided some weak evidence that the risk of psychosis proneness varied at the neighbourhood level ($P = 0.07$; Table 3). Following model building, we observed that the adjusted odds of UHR or FEP status, relative to controls, were similarly elevated in neighbourhoods characterised by greater proportions of single-parent households, lower deprivation and greater ethnic diversity (Table 3). For example, a one per cent increase in the proportion of single-parent households was associated with an increased adjusted odds ratio (aOR) of UHR status of 1.59 (95% CI: 0.99, 2.57; $P = 0.056$) and FEP status of 1.56 (95% CI: 1.00, 2.45;

© 2014 The Authors. Acta Psychiatrica Scandinavica Published by John Wiley & Sons Ltd.

Table 2. Clinical and sociodemographic sample characteristics, by participant status

Variable	People with FEP	UHR group	Controls	*P*-value*
Median age (IQR)	24.3 (21.3, 29.0)	20.5 (18.9, 22.8)	27.0 (23.0–32.0)	FEP vs. UHR: $P < 0.001$ FEP vs. control: $P = 0.02$ UHR vs. control: $P < 0.001$
Total participants ($N = 248$)	159	48	41	–
Men (*N*, %)	101 (63.5)	24 (50.0)	19 (46.3)	0.06^{C}
White British (*N*, %)	100 (62.9)	44 (91.7)	30 (73.2)	$<0.001^{C}$
Single† (*N*, %)	139 (87.4)	41 (85.4)	31 (75.6)	0.17^{C}
Socioeconomic status (*N*, %)				
Professional and managerial	18 (11.3)	6 (12.5)	15 (36.6)	0.003^{FE}
Intermediate and self-employed	23 (14.5)	6 (12.5)	9 (22.0)	
Semi-routine and routine	70 (44.0)	17 (35.4)	11 (26.8)	
Students	28 (17.6)	10 (20.8)	5 (12.2)	
LR unemployed	17 (10.7)	5 (10.4)	–	
Unclassifiable	3 (1.9)	4 (8.3)	1 (2.4)	
Parental socioeconomic status (*N*, %)				
Professional and managerial	47 (29.6)	26 (54.2)	17 (41.5)	0.04^{FE}
Intermediate and self-employed	34 (21.4)	10 (20.8)	11 (26.8)	
Routine and manual	46 (28.9)	6 (12.5)	10 (24.4)	
Students	2 (1.3)	–	–	
LR unemployed	9 (5.7)	4 (8.3)	–	
Unclassifiable	21 (13.2)	2 (4.2)	3 (7.3)	
Non-affective psychosis (F20–29)	131 (82.4)	–	–	–
Affective psychosis (F30–33)	28 (17.6)	–	–	–

FEP, first-episode psychosis; UHR, ultra-high risk; IQR, interquartile range.

*We used the Mann–Whitney *U*-test to inspect differences in median age between each pair of participant groups separately. For categorical variables, we used Chi-squared tests (superscript: C) or Fisher's exact tests (where any cell $n \leq 5$; superscript: FE) to inspect differences between the three groups simultaneously.

†Single included all single, widowed and divorced participants at assessment vs. people either married or in a civil partnership.

$P = 0.052$). The odds of UHR (aOR: 0.86; 95% CI: 0.76, 0.99; $P = 0.033$) and FEP status (aOR: 0.88; 95% CI: 0.78, 1.00; $P = 0.046$) also independently *decreased* with greater neighbourhood-level deprivation in our final model, while greater ethnic diversity increased the odds of membership in either the UHR (aOR: 1.28; 95% CI: 1.00, 1.64; $P = 0.046$) or FEP group (aOR: 1.28; 95% CI: 1.02, 1.59; $P = 0.030$). Individual-level socioeconomic status was also independently associated with greater odds of UHR and FEP status. These associations broadly held when non-affective and affective FEP were modelled as separate multinomial outcomes in the same model (Table 4).

Discussion

Key results

To our knowledge, this is the first study to have explored geographical and social differences in residential environments between people with FEP, UHR participants and a representative sample of controls. The spatial distribution of both the UHR and FEP group differed from controls, and for FEP participants, these differences were apparent for non-affective and affective psychotic disorders independently. This latter finding was unexpected given previous literature suggests an absence of neighbourhood-level variation in affective psychoses (1, 29). Although the spatial patterning of non-affective and affective psychotic disorders also differed from each other, risk appeared to be associated with the same set of neighbourhood-level social exposures. These factors, which included the proportion of single-parent households, deprivation and ethnic diversity, similarly predicted UHR status, raising the possibility that exposure to adverse environments may affect the population expression of psychosis from sub-threshold UHR criteria through to full psychotic disorder. Interestingly, these neighbourhood-level trends persisted despite control for several important individual-level confounders, including parental and participant socioeconomic position, ethnicity, age and sex.

Sources of possible bias

Controls were not identified via simple random sampling from across the CPFT catchment area, but by multistage sampling based on GP location. Nevertheless, they were broadly representative of the underlying population at risk in the catchment area on a range of measured covariates, including ethnicity, individual socioeconomic status and neighbourhood-level deprivation, inequality, ethnic segregation and the proportion of single-parent

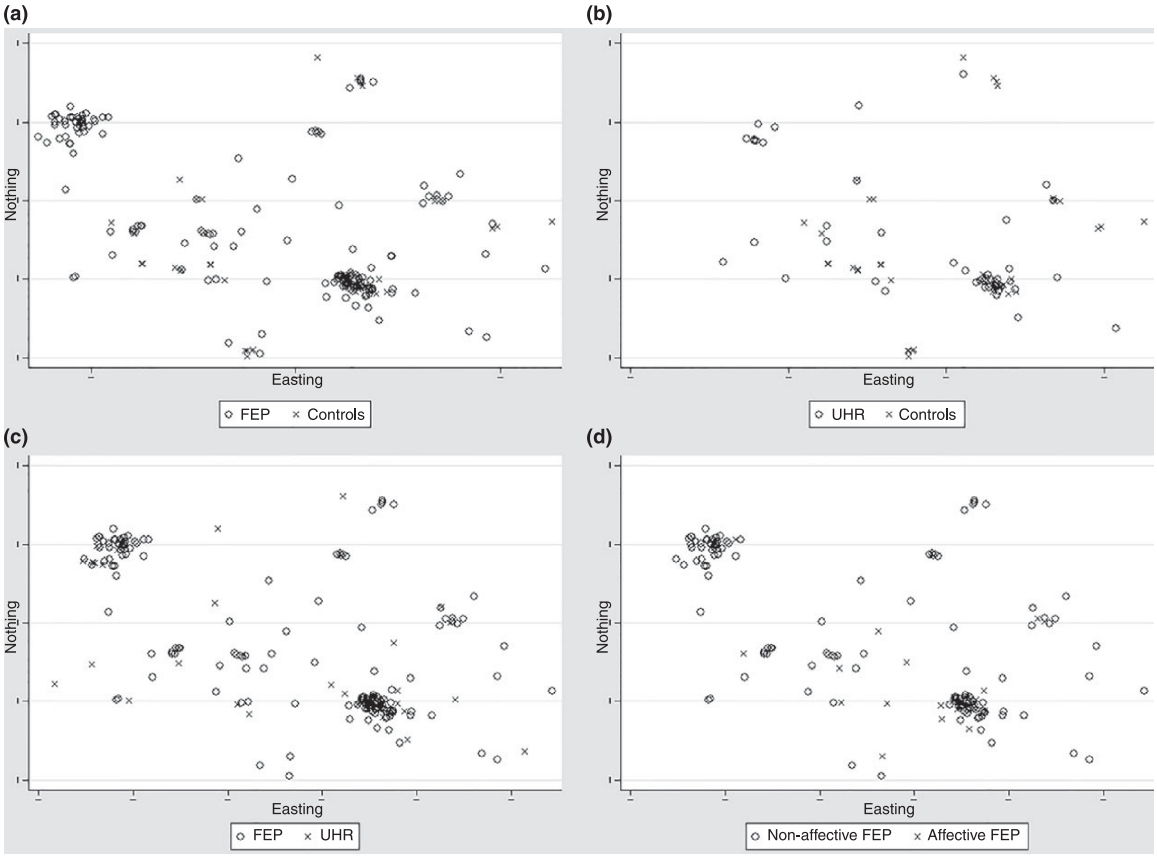


Fig. 1. Spatial locations of participants, by status. The spatial distribution of controls is significantly different to both people with (a) first-episode psychosis (FEP) ($P = 0.01$) and (b) the ultra-high risk (UHR) group ($P = 0.04$) under a two-dimensional *M*-test. There is no statistically significant difference in the spatial distribution of (c) FEP and UHR participants ($P = 0.17$). The spatial distribution of (d) people with non-affective and affective FEP were also significantly different from each other ($P = 0.01$). Locations are based on postcode centroid at first contact. Axis scales are plotted according to British National Grid coordinates of residential postcode at first contact, but the coordinates and scale have been removed to preserve sample anonymity.

households. Although controls from more urban populations were somewhat over-represented in our sample (indexed by greater population density, non-white British ethnic density and proportion of single-person households), incidence studies of FEP have shown that these neighbourhoods increase risk (4, 6, 7), so any bias would have made reported effect sizes conservative. Under *gsem,* we could not use probability weights to account for the multistage sampling design and associated non-response at each level of selection. However, this was possible via ordinary (i.e. single level) multinomial logistic regression with robust standard errors (adjusted for neighbourhood clustering); after calculating and including inverse probability weights for controls, all neighbourhood-level exposures remained statistically significant in our final model (data available from authors).

Ultra-high risk participants were treated according to initial status, regardless of later transition, which occurred in about 10% of participants over 12 months (30). We have previously described individual level correlates of transition in this sample (20, 30).

Chance and confounding

We had a relatively small sample of control and UHR participants, which may have limited power to detect certain effects, including random effects at the neighbourhood level (for which there was some support). We also had a very small sample of people with affective psychotic disorder, making findings with respect to this subgroup tentative. We did not have data on family history of psychiatric disorder in FEP or control participants, or cannabis use in our sample, two potentially important unmeasured confounders. Neighbourhood exposures were assessed cross-sectionally, based on residential neighbourhood at first contact; we were

© 2014 The Authors. Acta Psychiatrica Scandinavica Published by John Wiley & Sons Ltd.

Table 3. Adjusted odds of FEP or high-risk status vs. controls in final two-level multinomial model associated with individual- and neighbourhood-level exposures

	People with FEP aOR (95% CI)	UHR group aOR (95% CI)
Individual-level exposures		
Age (years)	0.94 (0.84, 1.07)	0.71 (0.60, 0.84)*
Men (vs. women)	2.03 (0.73, 5.64)	1.31 (0.40, 4.31)
BME status (vs. white British)†	0.72 (0.22, 2.45)	0.19 (0.04, 0.97)*
Single marital status (vs. married)	1.01 (0.25, 4.04)	0.23 (0.04, 1.34)
Socioeconomic status‡	1.79 (1.11, 2.88)*	1.78 (1.03, 3.08)*
Parental socioeconomic status‡	1.25 (0.89, 1.77)	0.95 (0.62, 1.44)
Neighbourhood-level exposures		
% Single-parent households	1.56 (1.00, 2.45)*	1.59 (0.99, 2.57)**
% Ethnic diversity	1.28 (1.02, 1.59)*	1.28 (1.00, 1.64)*
% Households in multiple deprivation	0.88 (0.78, 1.00)*	0.86 (0.76, 0.99)*
Neighbourhood-level random effects	Variance (SE)	Wald *P*-value
Null model	3.64 (2.03)	0.07
Individual-adjusted model	3.72 (2.20)	0.09
Fully adjusted model	2.58 (1.62)	0.11

FEP, first-episode psychosis; UHR, ultra-high risk; aOR, adjusted odds ratio; CI, confidence interval; BME, black and minority ethnic; SE, standard error.
†Due to the small sample of BME participants, models with a six-category ethnicity variable would not converge, and so the binary white British vs. BME variable was substituted.
‡aOR associated with one-category decline in socioeconomic status. LRT *P*-value suggested a model fitted with social class (participant and parental) categories as categorical indicator variables did not improve fit: $P = 0{\cdot}11$.
*$P < 0.05$; **$P < 0.10$.

Table 4. Adjusted odds ratios from re-fitted final two-level multinomial model with non-affective and affective FEP as separate outcomes

	Non-affective psychosis aOR (95% CI)	Affective psychosis aOR (95% CI)	UHR group aOR (95% CI)
Individual-level exposures			
Age (years)	0.96 (0.85, 1.09)	0.88 (0.75, 1.03)	0.71 (0.60, 0.84)*
Men (vs. women)	2.36 (0.84, 6.66)	1.13 (0.33, 3.90)	1.26 (0.38, 4.14)
BME status (vs. white British)†	0.65 (0.19, 2.25)	1.13 (0.27, 4.76)	0.20 (0.04, 1.02)**
Single marital status (vs. married)	1.10 (0.27, 4.54)	0.71 (0.12, 4.03)	0.23 (0.04, 1.32)**
Socioeconomic status‡	1.78 (1.10, 2.88)*	1.76 (0.98, 3.15)**	1.80 (1.04, 3.10)*
Parental socioeconomic status‡	1.32 (0.92, 1.86)	0.92 (0.59, 1.44)	0.92 (0.61, 1.41)
Neighbourhood-level exposures			
% Single-parent households	1.56 (0.99, 2.44)**	1.55 (0.95, 2.55)**	1.59 (0.99, 2.56)**
% Ethnic diversity	1.27 (1.02, 1.59)*	1.25 (0.98, 1.61)**	1.28 (1.00, 1.64)*
% Households in multiple deprivation	0.90 (0.79, 1.01)**	0.82 (0.71, 0.95)*	0.86 (0.75, 0.98)*

Neighbourhood-level random effects	Variance (SE)	Wald *P*-value
Null model	3.91 (2.18)	0.07
Model adjusted for individual effects	3.30 (1.94)	0.09
Fully adjusted model	2.54 (1.61)	0.11

UHR, ultra-high risk; aOR, adjusted odds ratios; CI, confidence interval; BME, black and minority ethnic; SE, standard error; FEP, first-episode psychosis.
†Due to the small sample of BME participants, models with a six-category ethnicity variable would not converge, and so the binary white British vs. BME variable was substituted.
‡aOR associated with one-category decline in socioeconomic status.
*$P < 0.05$; **$P < 0.10$.

unable to assess cumulative exposure to neighbourhood effects which may have accrued over the life course. Our study also had several strengths, including a robust FEP and UHR ascertainment procedure based on epidemiological principles and a tightly defined catchment area, and appropriate use of novel spatial and multilevel multinomial logistic regression models.

Interpretation

Our results support the possibility that people at UHR of psychosis are exposed to similar adverse neighbourhood conditions prior to transition as people already in their first episode, even after controlling for more direct markers of social disadvantage such as socioeconomic status. Relevant neighbourhood-level exposures identified in this study were related to both socioeconomic deprivation and social cohesion; the neighbourhood proportion of single-parent households may have been a proxy for deprivation, given substantial correlation between these exposures ($r = 0.66$). Having controlled for this, the counterintuitive negative association between multiple deprivation and psychosis proneness might indicate a nonlinear relationship between psychosis and deprivation (31). The observed association between psychosis proneness and greater neighbourhood ethnic diversity may have been a neighbourhood-level proxy for individual BME status, for which we had a small sample to detect variation in risk, but which is a well-established risk factor for psychotic disorders (32). It may also have been a proxy for lower neighbourhood-level ethnic density, given near-perfect negative correlation between the two ($r = -0.99$). Ethnic density attenuates schizophrenia risk in some ethnic groups (33), perhaps via greater social cohesion (6, 34) mediating the deleterious effects of discrimination (35, 36). Interestingly, both lower cohesion and greater discrimination have now been associated with risk of subthreshold psychosis (34, 35) and clinically relevant psychotic disorder (6, 36).

Several studies have demonstrated associations between urban birth, upbringing and later non-affective psychosis risk (8–10). These strengthen evidence for a causal relationship between disorder and aspects of the social environment, unless social

drift begins in the parental generation (or earlier); to our knowledge, no study has investigated the role of intergenerational social drift, although the over-representation of parents of UHR participants in our study in the highest socioeconomic category was not consistent with this. An alternative possibility is that UHR participants had already begun to experience social drift earlier in their prodrome; they experienced the biggest difference in social status of all three groups when compared to their parents' occupational position and there is evidence elsewhere that UHR groups already exhibit certain premorbid cognitive deficits (37). Unfortunately, we did not have sufficient longitudinal data on our UHR group to investigate neighbourhood residential changes over time in relation to risk of transition. Future prospective studies are now required to build on the small body of equivocal research on the risk of transition from UHR to FEP in relation to residential social environments (14, 15), in line with similar research which has addressed transition in relation to individual-level childhood adversities (38).

Our results have potential implications for aetiology, prevention and the provision of mental health services in terms of early intervention and early detection of psychosis. In addition to the concentration of psychosis risk in socially disadvantaged neighbourhoods determined aetiologically, duration of untreated psychosis may also be longer in these communities (39), potentially exacerbating prognosis in already disadvantaged groups. In public health terms, the debate over social drift vs. causation may be relatively sterile, given that our data, and that of others (39–41), suggest that our most disadvantaged and fragmented communities will shoulder a disproportionate burden of this population-level psychiatric morbidity, regardless of causality. From a public mental health perspective, identifying which aspects of neighbourhood social inequality increase the risk of transition to FEP or introduce delays to help-seeking will be important in designing effective early detection services and prevention strategies which target improvements in the long-term social and clinical outcomes for young people at risk of psychotic disorder.

Acknowledgements

Dr. James Kirkbride is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant number: 101272/Z/13/Z). Part of his contribution to this manuscript was also supported by a Sir Henry Wellcome Fellowship (Grant number: WT085540). Dr. Kirkbride had full access to all the data in the study and had final responsibility for the decision to submit for publication. This project also received support from European Community's Seventh Framework Programme under grant agreement No. HEALTH-F2-2010-241909 (Project EU-GEI). EU-GEI is the acronym of the project 'European network of National Schizophrenia Networks Studying Gene-Environment Interactions'. Peter Jones directs the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for Cambridgeshire & Peterborough and is supported by NIHR grant RP-PG-0606-1335. Funders had no involvement in the preparation of this manuscript. The authors thank the study teams of the SEPEA, PAATh and EU-GEI studies and all the members of the CAMEO services for their help and participation. We are grateful to the former Mental Health Research Network (now the Clinical Research Network East) for their assistance with this project.

Declarations of interest

None of the authors have any conflicts to declare in the past 2 years. A medical writer or editor was not used in the preparation of this manuscript.

References

1. March D, Hatch SL, Morgan C et al. Psychosis and place. Epidemiol Rev 2008;**30**:84–100.
2. McGrath J, Saha S, Welham J, el Saadi O, Maccauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004;**2**:1–22.
3. Kirkbride JB, Errazuriz A, Croudace TJ et al. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. PLoS ONE 2012;**7**: e31660.
4. Allardyce J, Boydell J, van Os J et al. Comparison of the incidence of schizophrenia in rural Dumfries and Galloway and urban Camberwell. Br J Psychiatry 2001;**179**: 335–339.
5. Hjern A, Wicks S, Dalman C. Social adversity contributes to high morbidity in psychoses in immigrants -a national cohort study of two generations of Swedish residents. Psychol Med 2004;**34**:1025–1033.
6. Kirkbride J, Boydell J, Ploubidis G et al. Testing the association between the incidence of schizophrenia and social capital in an urban area. Psychol Med 2008;**38**:1083–1094.
7. Kirkbride JB, Jones PB, Ullrich S, Coid JW. Social deprivation, inequality, and the neighborhood-level incidence of psychotic syndromes in East London. Schizophr Bull 2014;**40**:169–180.
8. Lewis G, David A, Andreasson S, Allebeck P. Schizophrenia and city life. Lancet 1992;**340**:137–140.
9. Marcelis M, Takei N, van Os J. Urbanization and risk for schizophrenia: does the effect operate before or around the time of illness onset? Psychol Med 1999;**29**: 1197–1203.
10. Mortensen PB, Pedersen CB, Westergaard T et al. Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med 1999;**340**:603–608.
11. Pruessner M, Iyer SN, Faridi K, Joober R, Malla AK. Stress and protective factors in individuals at ultra-high risk for psychosis, first episode psychosis and healthy controls. Schizophr Res 2011;**129**:29–35.
12. Velthorst E, Nelson B, O'Connor K et al. History of trauma and the association with baseline symptoms in an ultra-high risk for psychosis cohort. Psychiatry Res 2013;**210**:75–81.

© 2014 The Authors. Acta Psychiatrica Scandinavica Published by John Wiley & Sons Ltd.

13. Şahin S, Yüksel Ç, Güler J et al. The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia. Early Interv Psychiatry 2013;**7**:414–420.
14. Dragt S, Nieman DH, Veltman D et al. Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. Schizophr Res 2011;**125**:69–76.
15. Shah J, Eack SM, Montrose DM et al. Multivariate prediction of emerging psychosis in adolescents at high risk for schizophrenia. Schizophr Res 2012;**141**:189–196.
16. Kirkbride JB, Stubbins C, Jones PB. Psychosis incidence through the prism of early intervention services. Br J Psychiatry 2012;**200**:156–157.
17. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch Gen Psychiatry 1991;**48**:764–770.
18. Williams J, Farmer AE, Ackenheil M, Kaufmann CA, McGuffin P. A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system. Psychol Med 1996;**26**:775–783.
19. Craddock M, Asherson P, Owen MJ, Williams J, McGuffin P, Farmer AE. Concurrent validity of the OPCRIT diagnostic system. Comparison of OPCRIT diagnoses with consensus best-estimate lifetime diagnoses. Br J Psychiatry 1996;**169**:58–63.
20. Zimbrón J, Ruiz De Azúa S, Khandaker GM et al. Clinical and sociodemographic comparison of people at high-risk for psychosis and with first-episode psychosis. Acta Psychiatr Scand 2013;**127**:210–216.
21. Yung AR, Yuen HP, McGorry PD et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005;**39**: 964–971.
22. European Network of Schizophrenia Networks Studying Gene-Environment Interactions (EUGEI). Identifying gene–environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr Bull 2014;**40**:739–6.
23. Office for National Statistics. 2011 Census: Aggregate data (England and Wales) In: UK Data Service Support. This information is licensed under the terms of the Open Government Licence http://www.nationalarchives.gov.uk/doc/open-government-licence/version/2; 2011. Downloaded from http://infuse.mimas.ac.uk. Accessed 15th October, 2014.
24. Office for National Statistics. The National Statistics Socio-economic Classification (NS-SEC rebased on the SOC2010). ONS; 2010; Available from: http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec–rebased-on-soc2010–user-manual/index.html. Updated 2010; cited 2014 18 March.
25. Office for National Statistics. Table QS119EW: households by deprivation dimensions. In: Office for National Statistics, ed. Titchfield; 2011.
26. Simpson L. Ghettos of the mind: the empirical behaviour of indices of segregation and diversity. J R Stat Soc Ser A Stat Soc 2007;**170**:405–424.
27. Tebaldi P, Bonetti M, Pagano M. M statistic commands: interpoint distance distribution analysis. Stata J 2011;**11**: 271–289.
28. Bonetti M, Pagano M. The interpoint distance distribution as a descriptor of point patterns, with an application to spatial disease clustering. Stat Med 2005;**24**:753–773.
29. Pedersen CB, Mortensen PB. Urbanicity during upbringing and bipolar affective disorders in Denmark. Bipolar Disord 2006;**8**:242–247.
30. Hui C, Morcillo C, Russo DA et al. Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. Schizophr Res 2013;**148**: 175–180.
31. Croudace TJ, Kayne R, Jones PB, Harrison GL. Non-linear relationship between an index of social deprivation, psychiatric admission prevalence and the incidence of psychosis. Psychol Med 2000;**30**:177–185.
32. Cantor-Graae E, Selten J-P. Schizophrenia and migration: a meta-analysis and review. Am J Psychiatry 2005;**162**: 12–24.
33. Veling W, Susser E, Van Os J, Mackenbach JP, Selten J-P, Hoek HW. Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. Am J Psychiatry 2008;**165**:66–73.
34. Walder DJ, Faraone SV, Glatt SJ, Tsuang MT, Seidman LJ. Genetic liability, prenatal health, stress and family environment: risk factors in the Harvard Adolescent Family High Risk for Schizophrenia Study. Schizophr Res 2014;**157**:142–148.
35. Anglin D, Lighty Q, Greenspoon M, Ellman L. Racial discrimination is associated with distressing subthreshold positive psychotic symptoms among US urban ethnic minority young adults. Soc Psychiatry Psychiatr Epidemiol 2014;**03**:1–11.
36. Veling W, Selten J-P, Susser E, Laan W, Mackenbach JP, Hoek HW. Discrimination and the incidence of psychotic disorders among ethnic minorities in The Netherlands. Int J Epidemiol 2007;**36**:761–768.
37. Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatr Scand 2014;**130**:1–15.
38. Bechdolf A, Thompson A, Nelson B et al. Experience of trauma and conversion to psychosis in an ultra-high-risk (prodromal) group. Acta Psychiatr Scand 2010;**121**:377–384.
39. Broussard B, Kelley ME, Wan CR et al. Demographic, socio-environmental, and substance-related predictors of duration of untreated psychosis (DUP). Schizophr Res 2013;**148**:93–98.
40. Kirkbride JB. Hitting the floor: understanding migration patterns following the first episode of psychosis. Health Place 2014;**28**:150–152.
41. Ngamini Ngui A, Apparicio P, Fleury MJ et al. Spatio-temporal clustering of the incidence of schizophrenia in Quebec, Canada from 2004 to 2007. Spat Spatiotemporal Epidemiol 2013;**6**:37–47.

Appendix 5 Use of the theory of planned behaviour to assess factors influencing the identification of individuals at ultra-high risk for psychosis in primary care

Early Intervention IN PSYCHIATRY
First Impact Factor released in June 2010 and now listed in MEDLINE!

Early Intervention in Psychiatry 2012; **6**: 265–275 doi:10.1111/j.1751-7893.2011.00296.x

Original Article

Use of the theory of planned behaviour to assess factors influencing the identification of individuals at ultra-high risk for psychosis in primary care

Debra A. Russo,[1,2] Jan Stochl,[2] Tim J. Croudace,[2] Jonathan P. Graffy,[3] John Youens,[4] Peter B. Jones[1,2] and Jesus Perez[1,2]

Abstract

Aim: To design and assess the psychometric properties of a questionnaire to identify and measure factors that influence the identification of individuals at ultra-high risk for psychosis in primary care. It will inform the subsequent design of educational interventions to help general practitioners (GPs; primary care physicians) detect these individuals.

Methods: The questionnaire was developed using the theory of planned behaviour (TPB). A semistructured discussion group elicited beliefs underlying GPs' motivations to detect these individuals and informed the construction of a preliminary 106-item questionnaire incorporating all constructs outlined in the TPB. A pilot phase followed, involving 79 GPs from 38 practices across 12 counties in England, to define the determinants of intention to identify these individuals. A psychometric model of item response theory was used to identify which items could be removed.

Results: The final instrument comprised 73 items and showed acceptable reliability ($\alpha = 0.77$–0.87) for all direct measures. Path analysis models revealed that all the TPB measures significantly predicted intention. Subjective norm, reflecting perceived professional influence, was the strongest predictor of intention. Collectively, the direct measures explained 35% of the variance of intention to identify individuals at ultra-high risk for psychosis, indicating a good fit with the TPB model.

Conclusion: The TPB can be used to identify and measure factors that influence identification of individuals at ultra-high risk for psychosis in primary care.

[1]Cameo Early Intervention Services, Cambridgeshire and Peterborough NHS Foundation Trust, and [2]Department of Psychiatry, and [3]General Practice and Primary Care Research Unit, University of Cambridge, Cambridge, and [4]Bretton Medical Practice, Peterborough, UK

Corresponding author: Dr Jesus Perez, Block 7, Ida Darwin, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EE, UK. Email: jp440@cam.ac.uk

Received 5 May 2011; accepted 6 August 2011

Key words: early intervention, primary care, psychosis, questionnaire, ultra-high risk.

INTRODUCTION

A wealth of observational data indicates that the longer psychotic disorders are untreated the worse their prognosis.[1–3] The early identification and referral for treatment of people who might be at ultra-high risk for psychosis (UHR[4]) could reduce the duration of untreated psychosis (DUP)[5] and this is a desirable clinical behaviour in those who have the opportunity to refer.

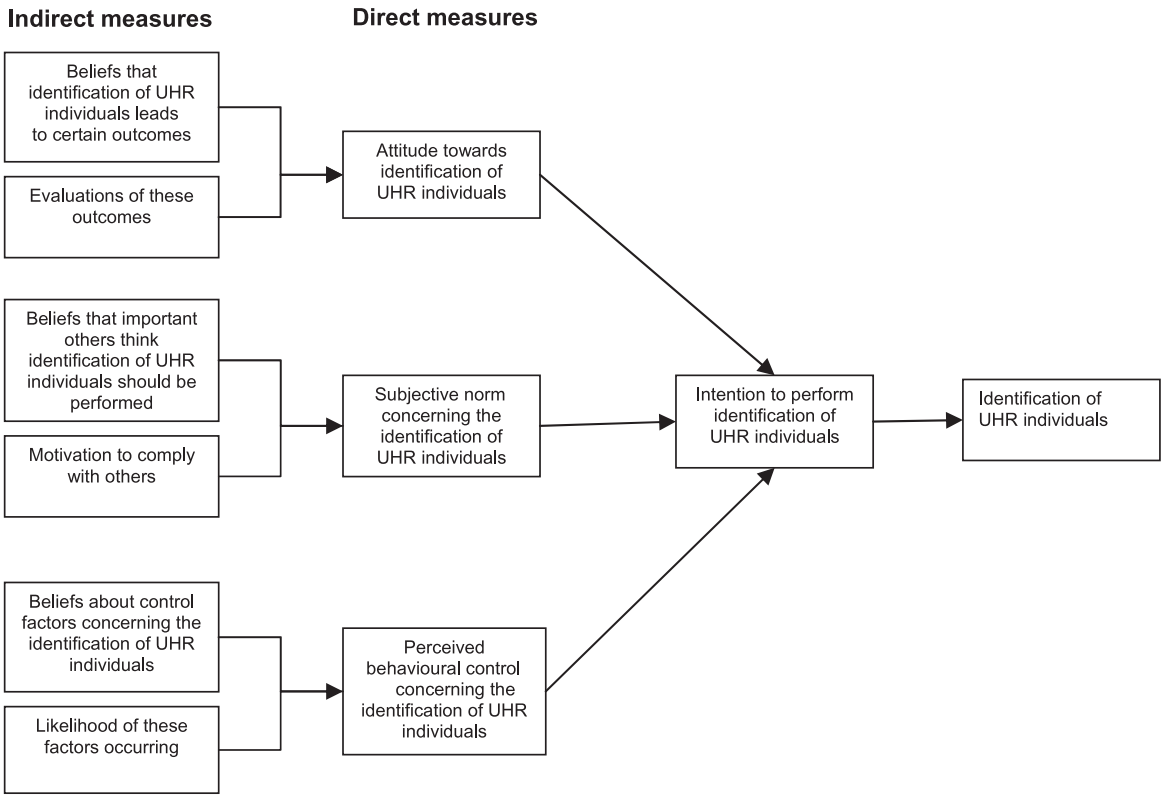
General practitioners (GPs; primary care physicians) are the professional group most commonly contacted first on the help-seeking pathway of UHR patients.[6] However, early detection of psychosis in primary care is difficult because of the non-specific nature of behavioural and psychological antecedents of psychosis and their very low predictive value.[7]

Some studies have suggested that GPs do not usually endorse continuing medical education in

© 2011 Blackwell Publishing Asia Pty Ltd

© 2011 Blackwell Publishing Asia Pty Ltd.

FIGURE 1. The theory of planned behaviour applied to the identification of ultra-high risk (UHR) for psychosis in primary care.



the early detection of psychotic disorders.[7] Moreover, education alone has failed to improve the management of mental health problems in primary care.[8] Indeed, a recent educational intervention in general practices that was intended to enhance awareness and skills in the detection of first-episode psychosis did not alter referral rates to specialized early intervention services or reduce DUP.[9] Thus, it is imperative to explore the factors that influence the identification of UHR for psychosis in primary care before attempting to design a programme to improve this aspect of care.

Interventions to change professional practice are often limited by the lack of an explicit theoretical and empirical basis.[10] The use of theory advances behavioural science[11] because it provides a generalizable framework for predicting and interpreting behaviour, informs the design of interventions and enables the evaluation of potential causal mechanisms.[12]

Theoretical framework

The theory of planned behaviour (TPB;[13,14]; Fig. 1) was selected because it provides clear definitions of constructs and is supported by a comprehensive body of correlational evidence.[15] The TPB assumes that the majority of human behaviour is goal directed, socially influenced[13] and that individuals are logical and rational in their decision making.[16] It is a deliberative processing model that implies individuals make behavioural decisions based on careful consideration of available information.[17] In addition, it recognizes the necessity of estimating the extent to which the individual is capable of exercising control over the behaviour in question.[18] The model's ability to consider internal (e.g. abilities; knowledge) and external (e.g. opportunity; cooperation of others) control factors in relation to performing a behaviour[19] is important in professional contexts such as National Health Service (NHS) primary care, where both factors may influence GPs' clinical behaviour.

The TPB proposes that the act of identifying individuals at UHR for psychosis in primary care is predicted by the strength of a GP's intention to identify these individuals. This intention is guided by three considerations: whether the GP is in favour of identification (attitude); the intensity of social pressure

© 2011 Blackwell Publishing Asia Pty Ltd

the GP perceives (subjective norm); and how much the GP feels in control of this identification (perceived behavioural control; PBC).

The TPB is acknowledged as an appropriate theory to predict health professional behaviour change[20] and offers insight into the processes underlying change in educational interventions in primary care.[21]

Aim

The aim of this study was to design and pilot items for a self-completion questionnaire to be used within primary care to identify and measure the factors that influence the identification of individuals at UHR for psychosis using TPB. This was undertaken as an initial phase recommended within the UK Medical Research Council framework[22] for the development and evaluation of a complex intervention. Results from this phase will inform the subsequent design of educational programmes for a cluster randomized controlled trial (RCT) that aims to evaluate the most effective way to help GPs identify these individuals.

METHODS

We followed the guidelines outlined by the co-author of the TPB[23] and reviews of current standard practice for its application.[17] We were also guided by recommendations from other researchers in this field.[24] The behaviour under investigation was defined as 'identifying individuals at UHR for psychosis during the consultation'.

Phase 1: Questionnaire development

Development of 'indirect' measures

The objective of this phase was to elicit commonly held beliefs about identifying UHR individuals from GPs. This enabled the development of questionnaire items based on these salient beliefs. Beliefs are central to the TPB; they provide the cognitive and affective foundations for attitudes, subjective norms and PBC.[23] An accurate understanding of the specific beliefs associated with identifying individuals at UHR for psychosis provides insight into why GPs may execute particular behaviours.[23] Therefore, this information can be important in the design of effective educational interventions.

Procedure. A semistructured discussion group was conducted to reveal salient beliefs underlying motivations to detect UHR individuals. A GP (JY) and advocate of the study chaired the group without the presence of researchers as it has been proposed that individuals may not want to disclose their genuine attitudes, or motivations to an unfamiliar moderator.[25] Also, group dynamics stimulate conversations and are especially effective for capturing information about social norms and opinions within a specific population.[26] The discussion group comprised of a convenience sample of eight GPs known to and selected by JY.

Analysis. Two researchers independently analyzed the responses that emerged from the discussion. The beliefs relating to attitude, subjective norm and PBC are summarized in Figure 2.

Following this stage, a questionnaire item was constructed to assess the strength of each behavioural, normative and control belief. Additionally, a corresponding item was developed to assess the impact each belief might have on identifying UHR individuals. These indirect items and their format were then agreed by the entire research team (including JY), to ensure that each belief was represented in the questionnaire (Table 1).

Development of 'direct' measures

Direct measures are a summary estimate of a GP's global attitude, subjective norm and PBC towards identifying individuals at UHR for psychosis, and predictors of intention to perform such identification.[24] Intention captures the motivational factors that influence behaviours[19] and signifies a GP's decision to exert effort to attempt identification.[14]

Procedure. Direct measures should be tailored to specific behaviours and samples under investigation.[24] This process should not be guided by an arbitrary selection of questions or adopted items from previous studies.[23] Therefore, appropriate items for the target population (GPs) and specific context (during a consultation in NHS primary care) were agreed by the research team to reflect each direct construct (Table 2).

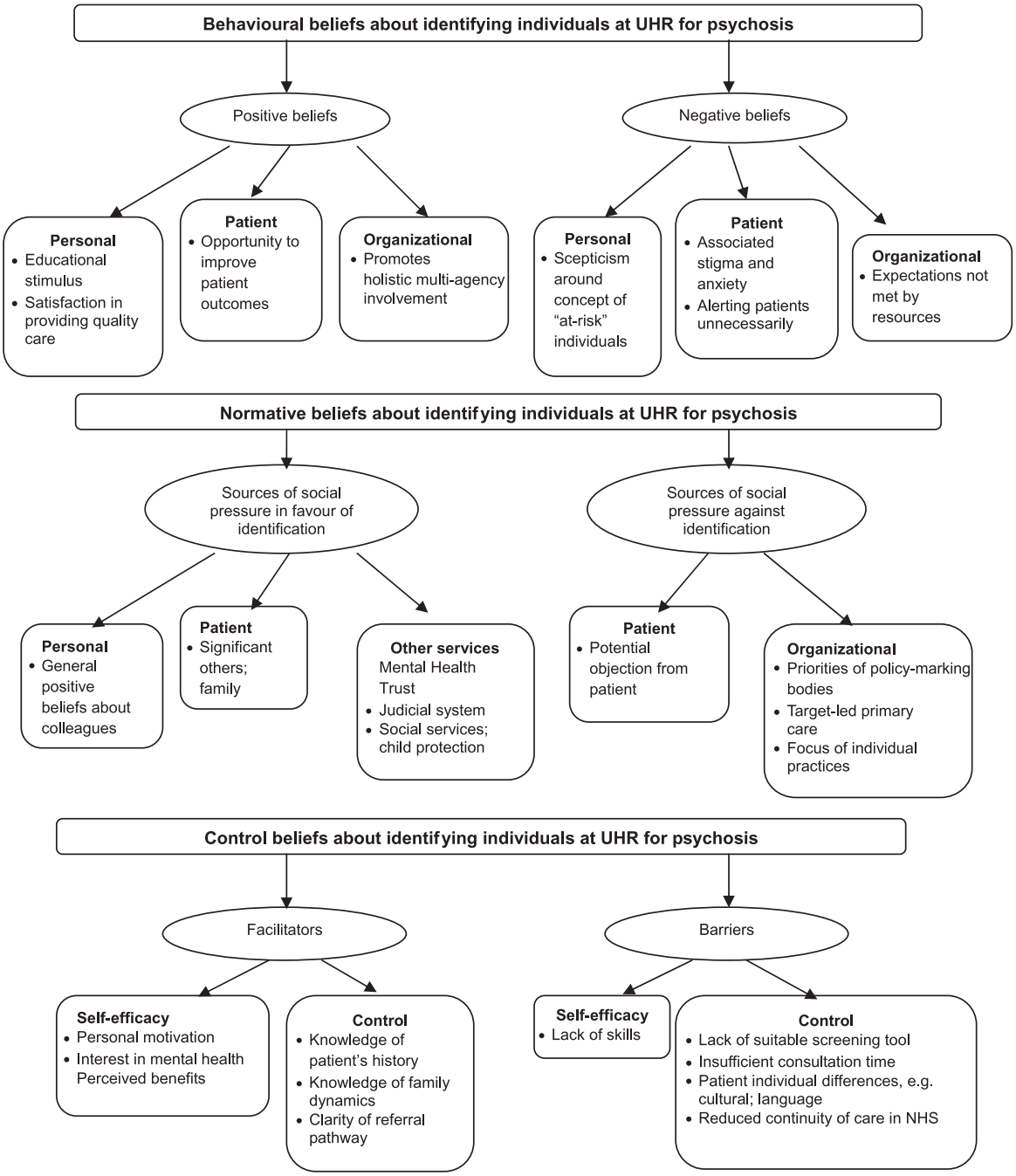
Phase 2: Questionnaire construction

A 106-item preliminary version of the questionnaire was constructed, including indirect and direct measures for attitude, subjective norm, PBC and intention. The questionnaire included instructions regarding its completion and an introduction about how an individual at UHR for psychosis might present in consultation. Feedback questions

© 2011 Blackwell Publishing Asia Pty Ltd

© 2011 Blackwell Publishing Asia Pty Ltd.

FIGURE 2. General practitioners' behavioural, normative and control beliefs elicited during the discussion group. NHS, National Health Service; UHR, ultra-high risk.



© 2011 Blackwell Publishing Asia Pty Ltd

TABLE 1. Examples of questionnaire items assessing indirect attitude, subjective norm and PBC

Belief strength	*n* items	Sample item	Impact of belief	*n* items	Sample item
Attitude	18	The labelling associated with the identification of patients at UHR for psychosis has a negative effect for the patient	Outcome evaluation for each attitudinal belief	18	Negative labelling for the patient is: *Extremely undesirable – extremely desirable*
Subjective norm	7	Other GPs do not attempt to identify patients at UHR for psychosis during the consultation	Motivation to comply with each group or individual	7	How much do you care what other GPs do? *Not at all – very much*
Perceived behavioural control	16	I lack the specific skills needed to identify a patient at UHR for psychosis during the consultation	The power each control belief exerts	16	Having the specific skills would make identification: *Less likely – more likely*

GPs, general practitioners; UHR, ultra-high risk.

TABLE 2. Examples of questionnaire items measuring direct attitude, subjective norm, PBC and intention

TPB construct		*n* items	Sample item
Attitude		9	Identifying a patient at UHR for psychosis during the consultation would be *harmful – beneficial*
Subjective norms		5	People whose views I value within my profession would not approve of me identifying patients at UHR for psychosis during the consultation: *Strongly agree – strongly disagree*
Perceived behavioural control	Self-efficacy	3	I could identify a patient at UHR for psychosis during the consultation without difficulty: *Strongly agree – strongly disagree*
Controllability		3	The decision to identify at UHR for psychosis during the consultation is beyond my control: *Strongly agree – strongly disagree*
Intention	Intention	3	I intend to identify patients at UHR for psychosis during the consultation: *Strongly agree – strongly disagree*
Self-prediction		1	I expect to identify patients at UHR for psychosis during the consultation: *Strongly agree – strongly disagree*

TPB, theory of planned behaviour; UHR, ultra-high risk.

concerning ambiguity, content, missing factors and format guided any necessary subsequent refinements. Finally, sociodemographic questions were added to describe the sample.

Phase 3: Questionnaire evaluation and refinement

The aim of this phase was to evaluate the acceptability and feasibility of administering the questionnaire within a representative sample of GPs in NHS primary care, in addition to evaluating its reliability.

Procedure

Questionnaires and information sheets were posted to 400 GPs working in 38 practices across 12 counties in England between September and November 2009. These practices were selected using maximum variation sampling and obtained from the NHS choices website (http://www.nhs.uk/servicedirectories/Pages/servicesearch.aspx). Selection criteria included: (i) surgeries with a minimum of five GPs; (ii) from different counties in an attempt to recruit a sample of GPs practising in geographically and socially diverse areas. A postal reminder was sent to non-respondents 3 weeks later.

Ethical approval was obtained as part of the National Institute for Health Research (NIHR) research programme RP-PG-0606-1335.

Analysis

A psychometric evaluation of the questionnaire was conducted to confirm that information obtained

© 2011 Blackwell Publishing Asia Pty Ltd

© 2011 Blackwell Publishing Asia Pty Ltd.

using a reduced-item final tool would still provide a sound basis for decision making.

A modern approach, in the form of a psychometric item response model – the polytomous graded response model[27] was used to examine the validity of each item within direct and indirect measures and to inform decisions regarding the removal of items. The internal consistency of the direct measures of attitude, subjective norm and PBC was assessed using Cronbach's alpha coefficient on both the original and reduced-item questionnaires. An internal consistency criterion is inappropriate for the evaluation of reliability of indirect measures[23] because they are formative rather than reflective indicators of the underlying construct.[28] Alternatively, correlations between direct and indirect measures of the same construct were calculated to confirm the convergent validity of the indirect measures. Confirmatory factor analysis[29] was conducted on all measures to assess the relative importance of each item on the total construct, thus confirming the structural conformity of the final questionnaire with the TPB. The relationship between intention and the indirect and direct measures were investigated using path analysis, with 'intention' specified as the dependent variable. Path analysis was used to reveal the degree of fit between the TPB and actual data, in addition to providing an estimation of multiple equation regression models linking the TPB variables.[30]

Data were analyzed using the statistical software package NCSS Version 7.1[31] for descriptive statistics; item analysis for the purpose of identifying redundant items for removal from the questionnaire was conducted using MULTILOG; and confirmatory factor analysis and path analysis was performed with Mplus Version 6.1 (Scientific Software International, Chicago, IL).[32]

RESULTS

Descriptive statistics of the respondents

Eighty-two (20.5%) GPs returned questionnaires. Due to incomplete fields, three questionnaires were excluded from the analyses. The mean time taken to complete the questionnaire was reported as 16.2 (standard deviation (SD) = 6.4) minutes. The mean age of participating GPs was 45.6 (SD = 9.4). Men (n = 42; 53%) and women (n = 37; 47%) were represented almost evenly in the sample. The mean number of years GPs had been practising was 16.4 (SD = 9.5). Approximately half (n = 40; 50.6%) of the sample reported attending some kind of mental health training during their careers. GPs reported seeing an average of 32 (SD = 9.3) patients per day and estimated that the mean number of patients they saw each day with a mental health problem was 7.5 (SD = 4.8).

Psychometric properties of the questionnaire

Validity

The polytomous graded response model[27] was used to study the validity of items within specific constructs. Also, distribution of responses for each item was assessed. This allowed the identification of items that required rewording, and those that were redundant because they added little information or offered similar response options. For the indirect measures, items were eliminated because of their ambiguity or similarity to other items. Final decisions on item exclusion were based on extensive discussions within the research team to avoid invalidation of the questionnaire due to exclusion of essential items that had emerged during the discussion group. Thirty-three items were excluded, resulting in a 73-item final questionnaire. Subsequent analyses were conducted on this reduced scale.

Pearson's correlations between the indirect and direct measures of the corresponding construct revealed each set of indirect beliefs was significantly correlated with their direct predictor of intentions: behavioural beliefs with attitudes (r = 0.54; P < 0.001); normative beliefs with subjective norms (r = 0.59; P < 0.001); and control beliefs with PBC (r = 0.52; P < 0.001). This suggests that indirect measures were well constructed and adequately covered the breadth of the measured construct.[33]

To assess the structural conformity of the final questionnaire with the TPB, factor analysis was used. The resulting coefficients can be interpreted as correlations between the measured construct and corresponding item. Higher coefficients indicate higher factor validity. Therefore, these items are superior at discriminating between GPs with low and high levels of the corresponding latent construct.

Table 3 shows the items with the highest factor validity within direct and indirect measures. Items within all direct measures, indirect attitude and subjective norm measured the corresponding construct satisfactorily; only one item within direct PBC and three items within indirect attitude showed a factor validity lower than 0.5. However, indirect PBC was less coherent. All items within this construct showed low intercorrelations, in accordance with

© 2011 Blackwell Publishing Asia Pty Ltd

TABLE 3. Items with the highest factor validity within indirect and direct measures.

Direct Measures		Item	Scoring	Factor Validity
Attitude		If I were to identify patients at UHR for psychosis during the consultation, it would be *Valuable/Worthless*	+1–+7	0.93
Subjective Norm		It is expected of me that I identify patients at UHR for psychosis during the consultation *Strongly Agree/Disagree*	+1–+7	0.83
Perceived Behavioural Control		I am confident that I could identify patients at UHR for psychosis during the consultation if I wanted to *Strongly Agree/Disagree*	+1–+7	0.95
Indirect Measures		**Item**	**Scoring**	**Factor Validity**
Attitude	Belief Strength	If I were to identify patients at UHR for psychosis during the consultation it would maintain their social functioning (e.g. support networks & relationships) *Strongly Agree/Disagree*	+1–+7	0.77
	Impact of Belief	Maintaining social functioning of patients is unimportant-important *Strongly Agree/Disagree*	–3–+3	
Subjective Norm	Belief Strength	Other GPs would approve of me identifying patients at UHR for psychosis during the consultation *Strongly Agree/Disagree*	–3–+3	0.87
	Impact of Belief	How much do you care what Other GPs think you should do? *Not at all/very much*	+1–+7	
Perceived Behavioural Control	Belief Strength	There is diversity in the cultural beliefs of my patients *Rarely/Frequently*	+1–+7	0.65
	Impact of Belief	For me, diversity in cultural beliefs would make identifying a patient at UHR for psychosis during the consultation *Difficult/Easier*	–3–+3	

GPs, general practitioners; UHR, ultra-high risk.

Ajzen's[23] premise that internal consistency is not a necessary feature of indirect measures. Therefore, factor analysis was not appropriate for this construct and the reported factor validity may not be a reliable figure.

Reliability

The lower bound estimates of internal consistency estimated by Cronbach's alpha for the original and reduced questionnaires are shown in Table 4. The values confirmed improvement for each of the constructs in the reduced version with the exception of that for intention which remained the same.

TABLE 4. Cronbach's alphas and standard errors of measurement (in brackets) for the direct measures of the original and reduced form questionnaires

Direct measures	Original questionnaire 106 items	Reduced questionnaire 73 items
Intention	0.87 (1.64)	0.87 (1.64)
Attitude	0.76 (3.18)	0.83 (2.71)
Subjective norms	0.64 (3.11)	0.74 (2.65)
PBC	0.58 (3.00)	0.72 (2.43)

PBC, perceived behavioural control.

Distribution of GPs' scores for all TPB constructs

Table 5 summarizes data obtained from the questionnaires. Higher scores indicate that a GP intends to, is in favour of, experiences social pressure to, and feels in control of identifying those who may be at UHR for psychosis.

For indirect measures, mean scores reflected overall positive attitudes towards favourable pressure to perform and control over the identification of individuals at UHR for psychosis. PBC was the lowest (6.1), which indicates a very weak level of positive control, and attitude the highest, but still showing a low score (71.0).

Mean scores for direct measures were above the mid-scale score for intention and attitude, and below the mid-scale score for subjective norm and PBC. This suggests that GPs considered identifying individuals at UHR for psychosis a worthwhile behaviour and would attempt identification in their practice, but that they believed that their peers might not approve this. In addition, their

© 2011 Blackwell Publishing Asia Pty Ltd

© 2011 Blackwell Publishing Asia Pty Ltd.

TABLE 5. Distribution of GPs' scores for all TPB constructs

Indirect measures	Final no. of items	Mean	Standard deviation	Standard error	Minimum score	Maximum score	Possible range of total scores
Attitude	18	71.0	31.4	3.53	–14	145	–378 to +378
Subjective norm	12	34.2	33.4	3.76	–19	117	–147 to +147
PBC	20	6.1	21.1	2.37	–39	63	–336 to +336
Direct measures	**Final no. of items**	**Mean**	**Standard deviation**	**Standard error**	**Minimum score**	**Maximum score**	**Mid-scale score**
Intention	4	21.2	4.7	0.53	6	28	16
Attitude	7	38.9	5.7	0.65	24	49	36
Subjective norm	4	17.8	4.6	0.52	6	28	20
PBC	8	23.5	4.2	0.47	13	35	24

PBC, perceived behavioural control.

confidence and control over identification was low.

Prediction of 'intention'

Path analysis revealed that all the direct measures of TPB significantly predicted intention. Subjective norm (perceived professional influences) was the strongest predictor of intention (regression coefficient = 0.41, $P < 0.001$), followed by attitude (0.30, $P < 0.01$) and PBC (0.22, $P < 0.01$). Collectively, the direct measures explained 35% of the variance of intention to identify UHR for psychosis.

DISCUSSION

The TPB was helpful in designing our questionnaire to expose and measure factors that might contribute to a GP's decision to attempt identification of an individual that may be at UHR for psychosis. Only by clearly understanding the motivations and barriers to this decision can we attempt to alter the identification behaviour and subsequently promote referral. The TPB facilitated the understanding of specific beliefs held by GPs concerning this identification. Beliefs elicited in the semistructured discussion group indicated that both internal and external factors contribute towards the decisions GPs make concerning identification. The responses that emerged from the discussion group revealed common influences for indirect belief-based measures; GPs expressed personal, patient and organizational related beliefs underlying their attitudes and subjective norms.

Improving outcomes emerged as the most important source of patient-related positive beliefs demonstrated by the items with the highest factor validity within the indirect attitude construct. Normative beliefs included perceived pressure for identification from colleagues and other services such as mental health teams and social services. The items with the highest factor validity within this construct indicated that most GPs perceived their behaviour in line with that of colleagues. However, GPs perceptions are not always accurate, since, in reality, their behaviour as a group varies considerably.[34] Providing GPs with more information about the actual norms of identification rates could be beneficial. The proposal that the *PBC* component should comprise separate measurement of controllability and self-efficacy[35] was supported by our study. Facilitators of self-efficacy included personal motivation, and an interest in mental health. Lack of skills was the main barrier to self-efficacy. Control factors were the major influence for PBC. Knowledge of the patient's personal and family background was an important facilitator of PBC.

These findings support previous work exposing the factors that might prevent GPs' incorporation of new knowledge and skills into their practice. Cabana *et al.*[36] identified lack of awareness, familiarity, agreement, self-efficacy and outcome expectancy, in addition to the inertia of previous practice, and external barriers as influential factors. This implies that the items included in our questionnaire reflect common concerns for many GPs within primary care and thus supports its validity.

Results from the analysis of the direct measures revealed that most GPs had positive intentions and attitudes towards identifying individuals at UHR for psychosis. Intentions to identify were most strongly predicted by subjective norms. This implies GPs' perceptions of whether other GPs identify UHR individuals; and whether significant others (e.g. patients, colleagues, health-care

© 2011 Blackwell Publishing Asia Pty Ltd

system) approve or disapprove of identification are prominent motivational factors. This notable influence of subjective norm on GP's behaviour has been found in previous studies.[37,38] Accordingly, effective interventions would need to prioritize the development of strategies that targeted this potential causal mechanism to prompt behavioural changes in this population.

Our questionnaire proved to be reliable, with the analysis supporting the predictive power of the TPB with regards to intention. The combination of attitude, subjective norm and PBC explained 35% of the variance of intention to identify individuals at UHR for psychosis. This is slightly lower than the average percentage (39%) of explained variance in intention reported for a variety of behaviours in the latest meta-analytic review of the TPB.[19]

Our findings may be limited by the use of self-reports as measures of beliefs and intention, and the omission of objective measures of the target behaviour. The latter will be addressed in a subsequent cluster RCT associated with this work. Physicians' self-reports on their practice tend to overestimate their adherence to guidelines[39] and it follows that GPs' self-reports of their beliefs associated with, and intentions to perform, identification of individuals at risk may also be subject to social desirability bias. This could threaten the validity of findings by obscuring relationships between variables. However, returned questionnaires were anonymous, with no incrimination or benefits from participating.

The low sample size ($n = 79$) and response rate (20.5%) from the invited sample ($n = 400$) was another limitation given that respondents may have differed systematically from non-respondents. There could be a case to validate the revised 73 item instrument in an independent sample.

A strength of this study is the thorough psychometric evaluation of our TPB questionnaire. Since the majority of TPB questionnaires are used only once with a specific population and behaviour, a thorough psychometric evaluation is usually considered non-feasible and therefore omitted.[40]

To our knowledge, this is the first study that has employed a theoretical framework to understand the factors that influence the identification of individuals at UHR for psychosis in primary care. To determine why interventions are unsuccessful or how successful interventions have their effect, we need to appreciate what variations of behavioural processes are responsible for any observed change.[41] As Ceccato *et al.*[42] argued, the utilization of behavioural theories to change clinical habits should guide all aspects of the intervention, that is development, dissemination, implementation and evaluation. The generalizability of results of atheoretical studies to primary care is questionable because they provide little information to guide the choice or optimize the components of complex interventions in clinical practice.

This research demonstrates how the TPB can be used to identify and measure factors that influence identification of individuals at UHR for psychosis in primary care. We have confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire to identify GPs' beliefs and intentions concerning the identification of individuals at UHR for psychosis. The information collated from the questionnaire will allow the identification of specific barriers that can be targeted with strategies designed to change primary care practice with respect to identifying UHR individuals. This could be important for improving referral pathways and reducing the duration of untreated psychosis. Michie *et al.*'s[43] work matching theoretically derived behavioural determinants with the most effective behaviour change techniques will facilitate the translation of this theoretically based causal model into a practical intervention to educate GPs in this area of mental health.

The recommendation that an original TPB questionnaire is developed every time a new behaviour is studied, or the same behaviour is studied with a new population[23] suggests similar methodology can be used to help GPs in the identification of other disorders and in a variety of mental health organizational environments.

A copy of the questionnaire is available at http://www.cameo.nhs.uk/Research/OngoingStudies/LEGSResearch/tabid/1445/language/en-GB/Default.aspx

ACKNOWLEDGEMENTS

PBJ, TJC, JPG and JP acknowledge funding support from NIHR programme grant RP-PG-0606-1335 'Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses'. TJC was supported by and DoH/NIHR Career Scientist Award in Public Health. The work forms part of the NIHR CLAHRC for Cambridgeshire and Peterborough. The authors would like to thank the LEGs research team: Carolyn Crane, Erica Jackson, Chris McAlinden, Gill Shelley and Michelle Painter, for their help and valuable comments in the development of questionnaire items from the discussion group data.

© 2011 Blackwell Publishing Asia Pty Ltd

© 2011 Blackwell Publishing Asia Pty Ltd.

REFERENCES

1. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005; **162**: 1785–804.
2. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2006; **62**: 975–83.
3. de Koning MB, Bloemen OJN, van Amelsvoort TAMJ *et al*. Early intervention in patients at ultra high risk of psychosis: benefits and risks. *Acta Psychiatr Scand* 2009; **119**: 426–42.
4. Yung AR. Commentary: the schizophrenia prodrome: a high-risk concept. *Schizophr Bull* 2003; **29**: 859–65.
5. Woods SW, Addington J, Cadenhead KS *et al*. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophr Bull* 2009; **35**: 894–908.
6. Platz C, Albrecht DS, Cattapan-Ludewig K *et al*. Help-seeking pathways in early psychosis. *Soc Psychiatry Psychiatr Epidemiol* 2006; **41**: 967–74.
7. Simon A, Lester HE, Tait L *et al*. The international study on general practitioners and early psychosis (IGPS). *Schizophr Res* 2009; **108**: 182–90.
8. Gilbody S, Whitty P, Grimshaw J, Thomas R. Educational and organisational interventions to improve the management of depression in primary care: a systematic review. *JAMA* 2003; **289**: 3145–51.
9. Lester HE, Birchwood M, Freemantle N, Michail M, Tait L. REDIRECT: cluster randomised controlled trial of GP training in first-episode psychosis. *Br J Gen Pract* 2009; **59**: 183–90.
10. Foy R, Francis JJ, Johnston M *et al*. The development of a theory-based intervention to promote appropriate disclosure of a diagnosis of dementia. *BMC Health Serv Res* 2007; **7**: 207. doi:10.1186/1472-6963-7-207.
11. Michie S, Prestwich A. Are interventions theory-based? Development of a theory coding scheme. *Health Psychol* 2010; **29**: 1–8.
12. Eccles M. The Improved Clinical Effectiveness through Behavioral Research Group (ICEBeRG). Designing theoretically-informed implementation interventions. *Implement Sci* 2006; **1**: 4. doi:10.1186/1748-5908-1-4.
13. Ajzen I. From intentions to action: a theory of planned behavior. In: Kuhl J, Beckman J, eds. *Action Control: From Cognitions to Behaviors*. New York: Springer, 1985; 11–39.
14. Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991; **50**: 179–211.
15. Skår S, Sniehotta FF, Araujo-Soares V, Molloy GJ. Prediction of behaviour vs. prediction of behaviour change: the role of motivational moderators in the theory of planned behaviour. *Appl Psychol-Int Rev* 2008; **57**: 609–27.
16. Sandberg T, Conner M. Anticipated regret as an additional predictor in the theory of planned behaviour: a meta-analysis. *Br J Soc Psychol* 2008; **47**: 589–606.
17. Conner M, Sparks P. Theory of planned behaviour and health behaviour. In: Conner M, Sparks P, eds. *Predicting Health Behaviour: Research and Practice with Social Cognition Models*, 2nd edn. Mainhead: Open University Press, 2005; 170–222.
18. Ajzen I, Madden TJ. Prediction of goal-directed behavior: attitudes, intentions, and perceived behavioral control. *J Exp Soc Psychol* 1986; **22**: 453–74.
19. Armitage CJ, Conner M. Efficacy of the theory of planned behavior: a meta-analytic review. *Br J Soc Psychol* 2001; **40**: 471–99.
20. Walker A, Watson M, Grimshaw J, Bond C. Applying the theory of planned behaviour to pharmacists' beliefs and intentions about the treatment of vaginal candidiasis with non-prescription medicines. *Fam Pract* 2004; **21**: 670–6.
21. Ramsay CR, Thomas RE, Croal BL, Grimshaw JM, Eccles MP. Using the theory of planned behaviour as a process evaluation tool in randomised trials of knowledge translation strategies: a case study from UK primary care. *Implement Sci* 2010; **5**: 71. doi:10.1186/1748-5908-5-71.
22. Medical Research Council. *Developing and Evaluating Complex Interventions: New Guidance*. London: MRC, 2008. [Cited 23 Feb 2009.] Available from URL: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC004871
23. Ajzen I. *Constructing a TpB Questionnaire: Conceptual and Methodological Considerations*, 2002, Revised January 2006. [Cited 24 Feb 2009.] Available from URL: http://www.people.umass.edu/aizen/pdf/tpb.measurement.pdf
24. Francis JJ, Eccles MP, Johnston M *et al*. *Constructing Questionnaires Based on the Theory of Planned Behaviour*. A Manual for Health Services Researchers. Centre for Health Services Research, University of Newcastle upon Tyne, UK, 2004. [Cited 23 Feb 2009.] Available from URL: http://people.umass.edu/aizen/pdf/Francis%20etal.TPB%20research%20manual.pdf
25. Kruger RA, Casey MA. *Focus Groups: A Practical Guide for Applied Research*. Thousand Oaks, CA: Sage Publications, 1994.
26. Kitzinger J. Introducing focus groups. *BMJ* 1995; **311**: 299–302.
27. Samejima F. Estimation of latent ability using a response pattern of graded scores. *Psychometrika Monogr Suppl* 1969; **34**: 100–14.
28. Conner M, Kirk S, Cade J, Barrett J. Why do women use dietary supplements? The use of the theory of planned behavior to explore beliefs about their use. *Soc Sci Med* 2001; **52**: 621–33.
29. Brown TA. *Confirmatory Factor Analysis for Applied Research*. New York: Guilford Press, 2006.
30. Wolfle LM. The introduction of path analysis to the social sciences, and some emergent themes: an annotated bibliography. *Struct Equation Model* 2003; **10**: 1–34.
31. Hintze J. NCSS (Version 7.1). NCSS, LLC. UT, Kaysville, 2008.
32. Muthén LK, Muthén BO. Mplus: statistical analysis with latent variables (Version 6.1). Los Angeles, CA, 1998–2010.
33. Francis J, Eccles M, Johnston M *et al*. Explaining the effects of an intervention designed to promote evidence-based diabetes care: a theory-based process evaluation of a pragmatic cluster randomised controlled trial. *Implement Sci* 2008; **3**: 50. doi:10.1186/1748-5908-3-50.
34. Green H, Johnston O, Cabrini S, Fornai G, Kendrick T. General practitioner attitudes towards referral of eating-disordered patients: a vignette study based on the theory of planned behaviour. *Ment Health Fam Med* 2008; **5**: 213–8.
35. Ajzen I. Perceived behavioral control, self-efficacy, locus of control, and the theory of planned behavior. *J Appl Soc Psychol* 2002; **32**: 665–83.
36. Cabana MD, Rand CS, Powe NR *et al*. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; **282**: 1458–65.
37. Limbert C, Lamb R. Doctors' use of clinical guidelines: two applications of the theory of planned behaviour. *Psychol Health Med* 2002; **7**: 301–10.
38. Godin G, Bélanger-Gravel A, Eccles M, Grimshaw J. Healthcare professionals' intentions and behaviours: a systematic review of studies based on social cognitive theories. *Implement Sci* 2008; **3**: 36. doi:10.1186/1748-5908-3-36.
39. Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. *Int J Qual Health Care* 1999; **11**: 187–92.

© 2011 Blackwell Publishing Asia Pty Ltd

40. French DP, Cooke R, McLean N, Williams M, Sutton S. What do people think about when they answer theory of planned behaviour questionnaires? A 'think aloud' study. *J Health Psychol* 2007; **12**: 672–87.
41. Michie S, Fixsen D, Grimshaw JM, Eccles MP. Specifying and reporting complex behaviour change interventions: the need for a scientific method. *Implement Sci* 2009; **4**: 40. doi:10.1186/1748-5908-4-4.
42. Ceccato NE, Ferris LE, Manuel D, Grimshaw JM. Adopting health behavior change theory throughout the clinical practice guideline process. *JCEHP* 2007; **27**: 201–7.
43. Michie S, Johnston M, Francis J, Hardemann W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. *Appl Psychol-Int Rev* 2008; **57**: 660–80.

© 2011 Blackwell Publishing Asia Pty Ltd

© 2011 Blackwell Publishing Asia Pty Ltd.

Appendix 6 Comparison of high and low intensity contact between secondary and primary care to detect people at ultra-high risk for psychosis: study protocol for a theory-based, cluster randomized controlled trial

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

STUDY PROTOCOL Open Access

Comparison of high and low intensity contact between secondary and primary care to detect people at ultra-high risk for psychosis: study protocol for a theory-based, cluster randomized controlled trial

Jesus Perez[1,2*], Debra A Russo[1,2], Jan Stochl[1,2], Sarah Byford[3], Jorge Zimbron[1,2], Jonathan P Graffy[4], Michelle Painter[1], Tim J Croudace[5] and Peter B Jones[1,2,6]

Abstract

Background: The early detection and referral to specialized services of young people at ultra-high risk (UHR) for psychosis may reduce the duration of untreated psychosis and, therefore, improve prognosis. General practitioners (GPs) are usually the healthcare professionals contacted first on the help-seeking pathway of these individuals.

Methods/Design: This is a cluster randomized controlled trial (cRCT) of primary care practices in Cambridgeshire and Peterborough, UK. Practices are randomly allocated into two groups in order to establish which is the most effective and cost-effective way to identify people at UHR for psychosis. One group will receive postal information about the local early intervention in psychosis service, including how to identify young people who may be in the early stages of a psychotic illness. The second group will receive the same information plus an additional, ongoing theory-based educational intervention with dedicated liaison practitioners to train clinical staff at each site. The primary outcome of this trial is count data over a 2-year period: the yield - number of UHR for psychosis referrals to a specialist early intervention in psychosis service - per primary care practice.

Discussion: There is little guidance on the essential components of effective and cost-effective educational interventions in primary mental health care. Furthermore, no study has demonstrated an effect of a theory-based intervention to help GPs identify young people at UHR for psychosis. This study protocol is underpinned by a robust scientific rationale that intends to address these limitations.

Trial registration: Current Controlled Trials ISRCTN70185866

Keywords: Early intervention, Primary care, Psychosis, Cluster randomized controlled trial, Ultra high-risk

* Correspondence: jp440@cam.ac.uk
[1]CAMEO Early Intervention Services, Cambridgeshire and Peterborough NHS Foundation Trust, Ida Darwin, Fulbourn, Block 7, Ida Darwin, Fulbourn, Cambridge CB21 5EE, UK
[2]Department of Psychiatry, Herchel Smith Building for Brain and Mind Sciences, University of Cambridge, Forvie Site, Robinson Way, Cambridge, UK
Full list of author information is available at the end of the article

© 2013 Perez et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

Background

The detection and prompt referral to early intervention services of young people who may be at ultra-high risk (UHR) for psychosis [1] is intended to reduce the duration of untreated psychosis (DUP) and improve outcomes [2]. Early referral is, therefore, a desirable behavior in professionals who have the opportunity to do so.

General practitioners (GPs; primary care physicians) are usually the healthcare professionals contacted first by individuals at UHR for psychosis [3]. However, early detection of psychosis in primary care is difficult because of the nonspecific nature of behavioral and psychological antecedents of psychosis, and the very low predictive value [4].

Some Scandinavian and Australian projects have developed protocols for the detection of people at UHR for psychosis in professional settings such as primary care [5,6]. However, none of them have evaluated the effectiveness or cost-effectiveness of different approaches. Such analyses may be important because education alone fails to improve the management and identification of mental health problems in primary care [7]. Indeed, a recent educational intervention that attempted to enhance GP skills in the identification of first-episode psychosis (FEP) neither modified referral rates to early intervention services nor reduced the DUP [8].

We present here the design and implementation of the first cluster randomized controlled trial (cRCT) that compares two different approaches to liaising with primary care, in order to increase detection of young people at UHR for psychosis and early referral to a specialist early intervention team. The approach and methodology follows the Medical Research Council (MRC), London, UK, guidelines for the design and evaluation of complex interventions [9].

Methods/Design

Cluster randomized controlled trial (cRCT)

Aim

To test the null hypothesis that a theory-based educational intervention for primary care, including ongoing personal liaison by specialist health professionals, is not different, in terms of effectiveness and cost-effectiveness, to a postal information campaign coordinated from an office in a specialist, secondary care-based, early intervention service (CAMEO, Cambridgeshire and Peterborough, UK; http://www.cameo.nhs.uk), for detecting individuals aged 16 to 35 years at UHR for psychosis in primary care.

In this cRCT, primary care practices across Cambridgeshire and Peterborough are allocated to one of the following educational groups and referral activity is followed over a period of 2 years:

1.) Low intensity: implementation of the postal information campaign that represents a minimum of good practice.
2.) High intensity: implementation of the postal information campaign plus an additional, ongoing theory-based educational intervention.

Identification and recruitment of practices

A total of 104 general practices, working across 138 surgeries (sites), within the geographical boundaries of Cambridgeshire and Peterborough, were identified from the Primary Care Research Network East of England (PCRN EoE; http://www.crncc.nihr.ac.uk/about_us/pcrn/eoe) database. All had practice nurses and varied from single-handed to multi-partner practices, with the largest practice having 15 GPs. They included a mixture of urban, suburban and rural practices.

The original design of the trial was predicated on the presumption that formal consent to take part in the study was not required because the study would not directly involve patients or their care, and was understood in the context of service development within the National Health Service (NHS) in primary care. Clinical equipoise was assumed and resource constraints precluded implementation in all practices. Thus, the trial would involve all practices across Cambridgeshire and Peterborough. However, the Cambridgeshire 1 Research Ethics Committee granted approval on the basis that consent was obtained from general practices to take part in the study, which represented a significant change in the design. Even if formal consent had not been required, the study team would still have needed the agreement of practices in the high intensity arm to undertake elements of the study, such as the educational sessions and distribution of leaflets among staff. The invitation to participate may therefore have influenced referral behavior in practices that did not consent to participate. We are, however, routinely collecting information regarding the number of UHR and FEP referrals from these sites as part of our ongoing clinical service evaluation. We will also analyze the characteristics of these practices in order to evaluate the validity of our findings.

Following the Ethics Committee's requirements, the partners at each practice were provided with an information sheet (available from the authors) detailing the study. They were then contacted by the PCRN EoE and research team, and asked whether they were interested in taking part. If they expressed interest, a liaison practitioner (LP) visited to obtain a signed consent form from the partner. A GP or nurse at the surgery (site) was identified to act as the point of contact should they be randomized to the high intensity arm.

All the clinical staff from practices randomized to the high intensity arm will be invited to attend educational

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

sessions organized at their respective surgeries, and their time reimbursed by the West Anglia Comprehensive Local Research Network (West Anglia CLRN; http://www.crncc.nihr.ac.uk/about_us/ccrn/west_anglia) as service time spent on the research.

Randomization of clusters

General practices were considered as the clusters and randomized at this level, since some practices operated from more than one surgery and shared clinical staff. Practices that consented to participate in the study were stratified according to three high-level factors that were considered, *a priori*, to be likely to relate to referral behavior:

1.) Three levels of geographical area: Cambridge and South Cambridgeshire, Huntingdon and East Cambridgeshire, and Peterborough and Fenland.
2.) GPs working at multiple sites (yes/no).
3.) Membership of the Association of Student Practices in Cambridge (N=8) where university students account for a high proportion (approximately 50%) of the total list size.

Randomized allocation was carried out independently of the research team and occurred after obtaining consent. Randomization was in 12 strata and 96 blocks, with block size 2 ('ralloc' command in Stata (StataCorp JP, College Station, TX, USA)) (Figure 1).

Primary outcome

The primary outcome of this cRCT is count data over a 2-year period: the yield - number of UHR for psychosis referrals to a specialist early intervention in psychosis service (CAMEO) - per practice site.

Secondary outcomes

New trial-initiated referrals will be assessed by the study team and stratified into individuals who meet criteria for UHR for psychosis or FEP according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) questionnaire (true positives) [10], and people who do not fulfill the criteria (false positives).

We will also perform an economic evaluation that will comprise two components:

1.) Evaluation of the short-run cost-effectiveness of both educational strategies in terms of incremental cost per true positive detected.
2.) Evaluation of longer-term cost-effectiveness using decision analytic techniques.

Data on resource use for costing purposes will be recorded using the Adult Service Use Schedule (AD-SUS) modified for early intervention (EI-ADSUS). The EI-ADSUS was designed on the basis of previous economic evidence in relevant mental health populations [11,12] and was adapted for early intervention following consultation with the clinical team and evidence from the literature [13].

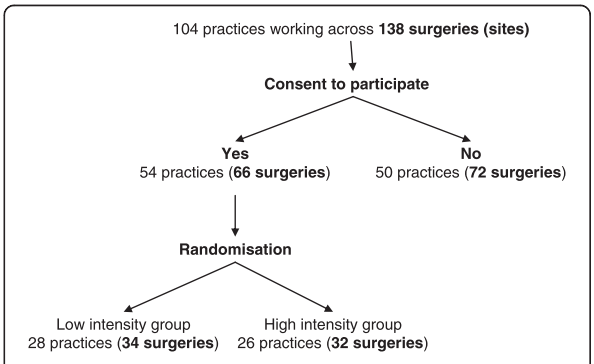


Figure 1 Flow of practices/surgeries through selection, consent and randomisation processes.

Sample size calculation

We powered the study based on sample size formulae for Poisson outcomes in a completely randomized design. For power of 80% with: 1) a significance level of 0.05 (two-sided); 2) referral counts expressed as an incidence rate of referrals in the low intensity group of 40 per 100,000 person-years [14]; 3) an anticipated incidence rate in the high intensity group of 0.00080 per 100,000 person-years; 4) 2,000 person-years per cluster (the average surgery list size for the age range of 16 to 35 years, per 2 years of study); and 5) a coefficient of variation estimated at a value of 0.15, our calculations required a sample size of 31 surgeries (practice sites) in each arm.

Statistical analysis

In the pre-modeling phase of our analysis, basic descriptive statistics for the total number of referrals, including proportion of true and false positives, will be provided. Subsequent analyses will be carried out separately for true and false positives.

Given that the outcomes are count data, our primary statistical method for modeling will be Poisson regression. If the assumptions of Poisson regression are not met (for example overdispersion), we will use zero-inflated or negative binomial regression models. The fit of the model to the data will be evaluated by comparison of model log-likelihoods. The results will be adjusted for surgery size, considering the number of GPs working in each site as a covariate in the model.

Economic analysis

The economic evaluation takes a broad public sector perspective, including the cost of all health and social

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

services, criminal justice sector costs, and productivity losses as a result of time off work due to illness. The high intensity intervention will be costed on the basis of contact data from records and the salary of the liaison practitioners delivering it, including employer costs (National Insurance and superannuation contributions) and overheads (capital, administrative and managerial) [15]. Other unit costs will be taken from published sources [15-19]. Productivity losses, for young people who are working, will be calculated using the human capital approach, which involves multiplying time off work due to illness by the participant's salary [20]. Analyses of total cost will compare mean costs using standard *t*-tests to enable inferences to be made about the arithmetic mean [21], and the validity of the results will be confirmed using bias-corrected, non-parametric bootstrapping [22].

Short-run cost-effectiveness will be assessed in terms of incremental cost per true positive and detected using the net benefit approach [23]. The incremental cost-effectiveness ratio (ICER) will be based on parameter estimates from bivariate random effects ('multilevel') models, which model costs and outcomes simultaneously, taking account of the hierarchical structure of the data in cluster randomized trials [24,25]. The parameters from the bivariate model will be used to construct cost-effectiveness acceptability curves (CEACs), a recommended decision-making approach, which describes uncertainty around the estimates of expected costs and effects. CEACs are presented by plotting the probability of the intervention being cost-effective for a range of possible values of willingness to pay for a unit improvement in outcome [26]. Since the short-term cost-effectiveness analysis focuses on identification of young people at risk, and not the outcomes for these individuals, decision analytic modeling will be used to explore the relative cost-effectiveness of the interventions in the longer-term [27]. Decision modeling allows assessment of the mean expected costs and outcomes for each arm of the study by modeling a hypothetical cohort of young people identified as at risk. The model will be populated using data on sensitivity and specificity from the cRCT, and data on longer-term care pathways, probabilities, costs and outcomes from a systematic review of the literature. Should gaps remain, expert opinion will be sought [28].

We will select the most suitable modeling framework in which to carry out the analysis, dependent upon the results of the cRCT and the availability of suitable data from the literature. In cases where individuals can be regarded as independent and interaction between them is not an issue in terms of the course or progression of an illness, as is the case in the current population, either a decision tree or a Markov model may be appropriate [29]. Model parameters will be entered into the model with associated probability distributions to explore uncertainty using Monte Carlo simulation, and probabilistic sensitivity analysis will be used to explore the robustness of the model and the impact of alternative model assumptions [27].

Low intensity: the postal information campaign

The main element of the postal information campaign is a specifically designed laminated leaflet (available from the authors), which provides guidelines to help GPs identify and refer individuals at UHR for psychosis. This leaflet will be posted to the surgeries in the low intensity group and integrated within the high intensity educational program ('high intensity intervention') to allow investigation of the research question.

Another leaflet had been in routine use for some years in CAMEO, but the trial presented an opportunity to revise it, while not radically changing routine practice in our particular early intervention service that is similar to other services in the region. For the design of the new leaflet, we followed a joint initiative from the MRC and British Psychological Society (BPS), UK, to examine the scientific understanding of the psychological processes involved in the implementation of evidence-based practice guidelines in health services. They recommended the following: 1) guidelines are more closely followed if the wording of behavioral instruction is concrete and precise; 2) the more precisely behaviors are specified, the more likely they are to be carried out; and 3) specifying what, who, when, where and how will assist implementation [30].

In addition, the research team collaborated with a designated advisory group of professionals, including psychologists, psychiatrists, NHS Trust communication teams and GPs. The consensus was that the leaflet should be A4 portrait and on one side only, brief and informative, and with the capacity to be used as a tool for identifying symptoms of individuals at UHR for psychosis. The leaflet was laminated for durability. Amendments and additions were incorporated through several cycles of drafting until a final agreement was reached.

The fundamental requirements were:

1.) An outline of the rationale for early detection of individuals at UHR for psychosis. This included points that were pertinent to GPs (for example halves the risk of suicide), as it has been shown that the more relevant or important the information is to the reader, the more likely they will spend time processing the information [31-34].
2.) A brief description of how individuals at UHR for psychosis might present and who to refer.

3.) Examples of questions for GPs to ask potential individuals at UHR for psychosis to help elicit vital information about underlying sub-threshold psychotic symptoms. This was designed to address Lester *et al.*'s (2005) important finding that GPs had concerns regarding how to phrase sensitive questions about hallucinations, thought disorder and suicide [35].
4.) A list of criteria that would indicate a referral. These were based upon the symptoms included in the CAARMS [10]. Items were presented in a tick-box format because it is well-documented that passive presenting of information is less effective than prompting individuals to engage with the material [36]. Additionally, the use of an algorithmic format has contributed to successful guideline use [37]. Special attention was paid to ensure that the criteria achieved a balance between sensitivity and specificity.
5.) Prominent contact details to facilitate referrals.

Design of the high intensity intervention

The MRC framework (2008) for the development and evaluation of a complex intervention was used to guide the development of the educational intervention [9]. We also referred to a review providing guidance on the essential components of an effective educational intervention in primary mental health care [32]. This recommended that learning components of the intervention should demonstrate a clinical need and facilitate practical application of new knowledge using examples and data from personal clinical practice. This is essential if clinicians are to recognize their potential needs for improvement. Also, interventions should be multifaceted and supported by practice-based contacts for a period of follow-up.

In conjunction with the factors outlined, we addressed the absence of an explicit, theoretical framework in the design of many educational interventions to change professional practice [38]. We considered the purpose of the intervention to be a change in behavior on the part of professionals.

Theoretical framework

There is growing evidence to support the application of psychological models of behavioral change to the clinical behavior of healthcare professionals [39,40]. It helps identify mediators of clinical decision-making [41], and thus allows appreciation of the causal mechanisms responsible for any observed behavior change and valid conclusions concerning the efficacy of the intervention [42].

The theory of planned behaviour (TPB) [43,44] was selected to underpin this research. The TPB is increasingly used to predict intentions and behavior in relation to clinical practice [45]. Ramsey *et al.* (2010) concluded that the TPB was an appropriate theory to predict healthcare professional behavior change and that it offered insight into the processes underlying change in educational interventions in primary care [46]. More pertinent to mental health issues, Green *et al.* (2008) found TPB predictors explained 86% of the variance in GPs' intentions to refer patients to specialist eating disorder services [47].

The TPB would propose that the act of identifying individuals at UHR for psychosis in primary care is predicted by the strength of a GP's intention to identify these individuals. This intention is influenced by three predictor variables: 1) whether the GP is in favor of identification (attitude); 2) the intensity of social pressure the GP perceives (subjective norm); and 3) how much the GP feels in control of this identification (perceived behavioral control (PBC)). The measurement of these predictors, pre- and post-intervention, and analysis of their relationship with our objective outcome measure (number of referrals), will enable evaluation of the effect of the intervention on actual behavior and the underlying behavioral process that drive it.

Feasibility of theory of planned behaviour (TPB) in primary care

Use of the TBP to design interventions requires the development of a questionnaire to allow the identification and measurement of specific beliefs associated with each construct (intention, attitude, subjective norm and PBC). These beliefs can then be targeted with strategies designed to influence these constructs in the appropriate direction. Strengthening practitioner intentions can be expected to change practitioner behavior in identifying individuals at risk.

In accordance with the TPB guidelines [48,49], pilot work was undertaken away from the study area to identify accessible behavioral, normative and control beliefs. This confirmed the feasibility, reliability and acceptability of administering a TPB-based questionnaire within a representative sample of GPs, to identify beliefs and intentions concerning the identification of individuals at UHR for psychosis. This development and the resulting questionnaire used in this trial are described in detail, elsewhere [50].

What TPB predictor variables will be targeted?

A crucial factor in the decision-making process of TPB variables to target was the experimental design of the trial. Strong internal validity is necessary to determine whether the intervention program affects the main outcome measure. If discrete cluster questionnaire scores for the TBP variables are taken into account and predictor variables are targeted accordingly, surgeries in the high intensity group would receive differing interventions. It

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

would then be impossible to make comparisons with the low intensity clusters, draw conclusions about the efficacy of the intervention and identify the potential causal mechanisms for any observed change. Furthermore, research has confirmed that simultaneous maximization of all three TPB variables generated the largest increase in intentions [51]. Therefore, it was decided that all three TPB predictor variables would be targeted for each surgery.

Selection of behavior change techniques for TPB predictor variables

We employed the TPB coding manual developed by Abraham and Michie (2008) [52] to match the three TPB predictor variables to the theoretical construct domains. We then used a tool developed by Michie *et al.* (2008) [53], which associates these theoretical constructs with the most effective behavior change techniques (Table 1).

Implementation of the high intensity intervention

Liaison practitioners (LPs)

Three dedicated LPs were specifically recruited for the trial to deliver the intervention (one male, two female; mean age 45.5 years, SD 4.7). All are experienced mental health professionals. Their principal function is to act as facilitator, since it is proposed that this is a fundamental role in helping individuals and teams to understand what they need to change, and how they need to change it, in order to translate evidence into practice [54]. Each LP is responsible for delivering the intervention to the surgeries within one of the three previously mentioned geographical boundaries in Cambridgeshire and Peterborough, regardless of the other two strata.

Components of the intervention

The educational components were designed to be multifaceted and combine different means of dissemination (for example DVD, PowerPoint (Microsoft, Redmond, WA, USA) presentation, paper-based printed material and outreach visits) as this strategy has been shown to be the most effective when attempting to change clinician behavior [32,34,55-57]. All the educational materials have a clear visual identity and incorporate a specifically designed trial logo, with a recognizable combination of colors that reflect CAMEO branding. This mainly attempts to create a connection between the trial and the GPs, and an association that prompts GPs to think about identifying individuals at UHR for psychosis.

According to the TPB, attitude, subjective norm and PBC towards identifying individuals at UHR for psychosis cannot be directly manipulated; changes in these predictor variables are assumed to follow from changes in salient beliefs associated with the target behavior [58,59]. Therefore, the behavioral, normative and control beliefs generated from the pilot study [50] guided the development of the materials and strategies included in the intervention. Lack of awareness, familiarity and agreement with the UHR for psychosis concept, self-efficacy and outcome expectancy, in addition to external barriers, and GPs' perceptions of what colleagues and significant others expected of them, will be targeted with theory-driven strategies throughout the intervention. The aim is to encourage GPs to identify individuals at UHR for psychosis by incorporating apposite knowledge and skills into their practice.

Duration of the intervention

The intervention will be implemented over a period of 2 years, since enhanced outcomes have been obtained with interventions that repeat activities and reminders at intermittent intervals [32]. Furthermore, previous research suggests that clinicians do not adopt research findings directly, but need time to process, assimilate and apply the information to their own needs and practice [60].

Educational sessions

Practice-based educational sessions were chosen since it has been suggested that outreach visits may be the most effective strategy in the introduction of new clinical guidelines and influencing professional behavior [32,57]. This would also allow comparisons of cost-effectiveness between a resource-intensive strategy and a simple postal campaign.

An initial 1-hour educational session on UHR for psychosis detection will be followed 1 year later by a booster 1-hour session to: reiterate the main messages; consolidate skills and knowledge; discuss particular practical scenarios which could emerge during the course of the study; and adjust or improve ongoing intensive liaison techniques if required. All three TPB predictor variables (that is attitude, subjective norms and PBC) and intention will be targeted in both educational sessions. Accordingly, the components of the first educational sessions will be:

1.) TPB questionnaire
the TPB questionnaire [52] will provide a measure of the proposed mechanisms that mediate GP's behaviour.
2.) PowerPoint presentation
the research team collaborated with the designated advisory group to generate and agree the content, format and layout of the presentation. A script was produced to ensure all LPs delivered the same content to each surgery. The presentation will cover the following items: a) the trial; b) the benefits of early detection for psychosis; c) the role of GPs in

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

Table 1 Behavior change techniques to facilitate theory of planned behavior (TPB) constructs throughout the trial

TPB construct	Behavior change technique	Procedures and materials	Delivery context
Attitude	Provide general information on behavior-benefit link	Leaflet: distributed by post, one for each GP in each surgery. Outline the benefits of the early detection of psychosis.	Pre-sessions 1 and 2
		PowerPoint presentation: provide information about physical, psychological and social benefits of identifying potential individuals at UHR for psychosis.	Sessions 1 and 2
		DVD: the above points are reiterated by the head of the department of psychiatry, a well-respected authority in the trial's area.	Session 2
	Provide information on consequences	PowerPoint presentation: provide information on the consequences of employing a 'wait and see' strategy with potential individuals at UHR for psychosis; reducing involvement with police and/or hospital admissions that often occur prior to a FEP.	Sessions 1 and 2
		DVD: include a vignette showing the possible consequences of a GP employing a 'wait and see' strategy with a individual at UHR for psychosis.	Session 2
	Provide information about personal susceptibility to negative consequences	PowerPoint presentation: provide peer-reviewed research evidence showing the importance of GPs in the care pathway of individuals at UHR for psychosis; linking with the potential costs of inaction by the GP.	Sessions 1 and 2
	Provide information about severity of health consequences	Leaflet: outline the potential to reduce suicide attempts.	Pre-sessions 1 and 2
		PowerPoint presentation: outline the link between delayed detection and transition to FEP; provide research data showing the poor outcomes for individuals who transition.	Sessions 1 and 2
		DVD: the above points are reiterated by the head of the department of psychiatry.	Session 2
Subjective norm	Provide information about others' approval	Produce newsletter for dissemination to each GP in all surgeries via post and email.	3 × yearly throughout the trial
		Include details of the number of surgeries participating and positive quotes from GPs about the consequences of participating in the trial.	
	Provide normative information about others' behavior	Produce newsletter for dissemination to each GP in all surgeries via post and email.	3 × yearly throughout the trial
		Include information about the number of surgeries participating in the trial.	
		Provide an update of the number of referrals in the trial, and true UHR and FEP cases in the county.	
	Prompt identification as role model/position advocate	Identify a LEGS 'champion' within each surgery to promote the identification of individuals at UHR for psychosis and raise any issues or problems at weekly meetings.	Post-session 1
	Provide opportunities for social comparison	Opportunities for peer interactions are facilitated by the group setting, and encouraged by LPs concerning potential advantages and facilitators of the identification of individuals at UHR for psychosis.	Sessions 1 and 2
		Opportunities for peer interactions are facilitated by the group setting and encouraged by LPs concerning previous referrals, sharing experience and discussing helpful strategies.	Session 2

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

Table 1 Behavior change techniques to facilitate theory of planned behavior (TPB) constructs throughout the trial *(Continued)*

		Group discussions and LPs reinforce social approval of the identification of individuals at UHR for psychosis.	Sessions 1 and 2
	Prompt barrier identification	Barrier identification based on responses to the PBC items within the TPB questionnaire.	Sessions 1 and 2
		Group discussions of possible barriers and means to minimize or address them.	Sessions 1 and 2
		Provision of strategies to overcome barriers, for example educate GPs to ask the most relevant questions to identify UHR for psychosis; therefore, making optimal use of the limited consultation time.	Sessions 1 and 2; and throughout the trial when appropriate during telephone and face-to-face contact with GPs
	Provide general encouragement	LPs to provide general encouragement on a one-to-one basis, as and when needed, and during the educational sessions to the surgery as a whole.	Throughout the trial during telephone and face-to-face contact with GPs
	Provide instruction	PowerPoint presentation: instruction on the appropriate questions to ask potential individuals at UHR for psychosis; how to refer, care pathway slide.	Session 1
		Leaflet: include examples of the questions to ask patients and tick-box options of the appropriate criteria required for a referral.	Pre-sessions 1 and 2
		DVD: outline in more detail the early signs and symptoms to be aware of, examples of questions, and how to refer using a question and answer format, with a GP and the head of the department of psychiatry.	Session 2
Perceived behavioral control (PBC)	Model/demonstrate the behavior	DVD: instructional vignettes showing examples of a GP conducting a consultation with a potential individual at UHR for psychosis, before and after the educational sessions.	Session 2
	Provide feedback on performance	Provided for each GP for every referral, both verbally and in a letter; include detailed feedback on the outcome of the initial assessment to explain why, or why not, the individual met the criteria for UHR for psychosis.	Throughout the trial
		PowerPoint presentation: feedback table for the previous year's referrals associated with each surgery, including source, outcome and any signposting to other services. Facilitate discussion around the reasons why they did, or did not, meet criteria.	Session 2
	Prompt practice	LPs to prompt practice on a one-to-one basis, as and when needed, and during the educational sessions to the surgery as a whole.	Throughout the trial during telephone and face-to-face contact with GPs
	Use of follow-up prompts	Leaflet: use as a reminder to prompt practice.	Pre-sessions 1 and 2
		Newsletter: use as a reminder to prompt practice.	3 × yearly throughout the trial
	Time management	Leaflet: strategy for optimal use of the limited consultation time.	Pre-sessions 1 and 2
		PowerPoint presentation: strategy for optimal use of the limited consultation time.	Session 1
		DVD: strategy for optimal use of the limited consultation time.	Session 2
	Prompting focus on past success	PowerPoint presentation: feedback table for the previous year's referrals associated with each surgery, prompting focus on the appropriate referrals to increase PBC.	Session 2; and when appropriate during telephone and face-to-face contact with GPs

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

Table 1 Behavior change techniques to facilitate theory of planned behavior (TPB) constructs throughout the trial *(Continued)*

	Provision of general information	General introduction to rationale and aims of the trial.	Sessions 1 and 2
		General introduction to UHR for psychosis definitions and concepts.	
		Information about the early detection-improved outcomes link.	
		Illustrate the parallels between the trial's aims and NICE recommendations for early intervention.	
Intention	Prompt general goal-setting and behavioral resolution	Encourage use of leaflet: prompt GPs to develop strategies to help remind them to use the leaflet for potential individuals at UHR for psychosis.	Sessions 1 and 2; and throughout the program, every time contact is made with the GP
	Prompt review of behavioral goals	GPs are asked to review a list of possible goals or plans they may have used to prompt or instigate the process of identification of individuals at UHR for psychosis, and indicate which strategies they used in the last year and which strategies would be useful in the following year.	Included within TPB questionnaire in session 2; and a copy provided for each GP for future reference

Based on Michie *et al.* (2008) [53]. *FEP* first-episode psychosis, *GP* general practitioner, *LEGS* liaison with education and general practices, *LP* liaison practitioner, *NICE* National Institute for Health and Care Excellence, *PBC* perceived behavioral control, *TPB* theory of planned behaviour, *UHR* ultra-high risk.

the trial; d) presentation of individuals at UHR for psychosis in general practice; e) referral procedure to CAMEO; and f) time to raise questions and discuss potential problems.

3.) Pack
while passive dissemination of printed educational materials alone have little effect on changing clinician behavior [32,34,61], Wensing and Grol (2005) proposed that they can reinforce outreach educational strategies by addressing barriers to change, and consequently facilitate modifications in clinicians' behavior [56]. Therefore, an information pack will be provided for each GP, including handouts of presentation notes, a reference list, paper copies of the trial leaflet, local early intervention services leaflet, a copy of the trial information sheet and contact details of the surgery's designated LP.

The second educational session will include:

1.) TPB questionnaire
it will contain an additional item in the questionnaire to help target the TPB variable intention. GPs will be asked to indicate which strategies they used in the last year and which strategies would be useful in the following year.

2.) PowerPoint presentation
the second presentation will include a brief recap of salient points covered in first session, feedback and a review of the practice's referral history to CAMEO since the trial began. As Howe *et al.* (2006) identified that successful educational interventions conducted in primary mental health care used personalized material and data based on the clinicians' own performance and/or patients [32], LPs will prompt discussion to actively involve GPs in an examination of their referral history, and consider problems and implications for their clinical practice.

3.) DVD
a video was well-received in an educational intervention to improve detection of FEP in primary care [35]. Therefore, an educational DVD was produced for the present trial, incorporating some of their ideas and techniques, together with novel approaches more relevant to our target population and topic. In conjunction with a broadcast media developer from the Media and Systems Group within the Anglia Support Partnership, Huntingdon, UK, and the designated advisory group, the research team developed an 18-minute DVD.
Considering that vicarious experience of a required behavior has been shown to increase self-efficacy [62,63], observing another GP implementing successful UHR for psychosis identification can demonstrate that it is achievable and might motivate GPs to attempt the same. The educational DVD was designed to provide this experience to GPs in the trial by depicting GP consultations with potential individuals at UHR for psychosis.
Opinion leaders can be persuasive agents of behavioral change [64]. These individuals are defined as credible individuals within a particular social and professional network who have significant influence over others [65]. Thus, Professor Peter B Jones (PBJ), Head of the Department of Psychiatry,

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

University of Cambridge, Cambridge, UK, presented the DVD. Actors were used to portray the roles of the GP (an occupational therapist) and patient (a research facilitator from the East Anglia Hub of the Mental Health Research Network (MHRN)). The DVD was filmed in and around a local general practice surgery for authenticity.

The content of the DVD included an introduction by PBJ explaining the concept of UHR for psychosis and emphasized the importance of early detection to improve outcomes, outlining the key role of GPs. Two consultation scenarios were used to reinforce the need to lower clinical threshold and consider the possibility of sub-threshold psychotic symptoms underlying precursors such as reduced functioning, poor sleep etc. The first scenario depicts a young person experiencing negative thoughts and perceiving individuals laughing at her and calling her derogatory names, but presenting to the GP with concentration and sleep problems which result in difficulties keeping up with college work. The GP employs a "watch & wait" strategy by asking the patient to return in several weeks. The second scenario depicts the same patient with the same symptoms. This time, the GP asks the supplementary questions provided on the leaflet and emphasised in the educational content. UHR symptoms are elicited and a referral is made to CAMEO for further assessment.

The scenarios were interspersed with short discussion segments by PBJ to emphasize and reiterate the salient points, and a question and answer session between the GP and PBJ to address prevalent beliefs elicited in the pilot questionnaire [50], for example why should a 'wait and see' strategy be avoided?

4.) Pack

in addition to the relevant information for this second session, a copy of the above mentioned DVD will be included.

Written feedback for every referral

In order to provide personalized feedback, GPs in the high intensity group will receive a more detailed written feedback for every assessment throughout the trial period. A template was designed to ensure consistency and accuracy. This described the outcome of the CAARMS and why, or why not, the patient did, or did not, meet the criteria for UHR for psychosis.

Ongoing support

Repeated contact and reminders appear to be more important in provoking a change in GP behavior than total time input [32,34]. Indeed, the effect of outreach can double with just one repeat contact [61]. In order to continue the intervention between and after the two sessions, every practice will be offered support and training in the form and frequency that best suits their particular needs, based on the information collected from the sessions.

Newsletter

Results from the pilot study [50] revealed that intentions to identify individuals at UHR for psychosis were most strongly predicted by subjective norms. This implies GPs' perceptions of whether other GPs identify individuals at risk, and whether colleagues or the healthcare system approve, or disapprove, of UHR for psychosis identification, are prominent motivational factors. Therefore, a regular newsletter reporting the participation rates and referral rates for the whole trial area was chosen as a strategy to target this potential causal mechanism to prompt behavioral change.

The thrice yearly newsletter will include graphs to present: 1) the number of referrals that met the criteria for FEP and UHR for psychosis for each of the geographical areas within the county; and 2) a comparison of the number of referrals from primary care and secondary care. This will demonstrate to GPs that other surgeries may also be referring individuals at UHR for psychosis to the trial, while raising awareness that there may be individuals at UHR for psychosis reaching secondary care services before referral to CAMEO.

Feedback questionnaire

To enable assessment of the acceptability and perceived effectiveness of the first year's intervention on GP learning, a feedback questionnaire will be sent to each GP 1 month before the second session is due. This information will also be used to tailor the second year of the intervention to include strategies that focus on the needs of individual surgeries, because the closer educational material is connected to real problems, the greater the application of new learning [32,33].

Completion of the intervention

The main outcome measure will enable assessment of changes in behavior and allow conclusions to be drawn concerning the efficacy of the educational intervention. However, supplementary evaluation information is beneficial to summarize the spectrum of knowledge, skills and attitudes learned, and also appreciate the suitability and appropriateness (feasibility and acceptability) of replicating the intervention in other settings [46]. To obtain this information, GPs will be asked to complete a second, more comprehensive feedback questionnaire at the end of the intervention. This will contain items to evaluate each of the intervention components and assess

Perez *et al. Trials* 2013, **14**:222
http://www.trialsjournal.com/content/14/1/222

relevance of the intervention, in addition to satisfaction and enjoyment.

Discussion

There is little definitive guidance on the essential components of an effective educational intervention in primary mental health care. Lester *et al.* (2009) designed an educational intervention for GPs addressing knowledge, skills and attitude about FEPs [8]. Results indicated that training is insufficient to alter referral rates to early intervention services or reduce the DUP. This is not an unusual phenomenon; many well designed studies with demanding training interventions in primary care mental health failed to show significant outcomes [32].

Power *et al.* (2007) reported results for an intervention comprising GP education and direct access to an early detection assessment team [66]. In contrast to Lester *et al.* (2009) [8], this intervention significantly increased referral of patients directly to mental health services; fewer patients experienced long delays in receiving treatment, compared with the control group receiving standard local mental health services without the addition of GP training [66]. Most recently, Simon *et al.* (2010) used a sensitization model to increase GPs' awareness of the warning signs in prodromal schizophrenia; three sets of clinical vignettes were sent by post to a randomly selected group of GPs in Switzerland. Results showed that sensitized GPs demonstrated a significant increase in diagnostic knowledge at 6 and 12 months, compared with both baseline knowledge scores and to GPs who were not sent the materials [67]. However, this study did not assess whether an increase in diagnostic knowledge resulted in a change in behavior in terms of more accurate or increased referrals to secondary care services.

Furthermore, the lack of an explicit theoretical framework in the designs of these three studies precluded appreciation of the causal mechanisms responsible for the observed improvement and valid conclusions concerning the efficacy of the intervention. Darker *et al.* (2010) claimed that the TPB has rarely been used to develop, design and evaluate interventions [68].

To our knowledge, no study has demonstrated an effect of a TPB-based intervention to help GPs identify people at UHR for psychosis on objectively measured behavior or examined whether the TPB constructs mediate the effects of an intervention on this behavior.

This cRCT attempts to address these limitations, ensuring that the intervention is underpinned by a robust scientific rationale which enables explanation of how and why each component of the intervention has any effect. This theoretical framework will also guide the process for evaluation and refinement of the intervention.

Status of the trial

The trial has begun and general practices have been randomly allocated to the high or low intensity arms.

Abbreviations

BPS: British psychological society; CAARMS: Comprehensive assessment of at-risk-mental-states; cRCT: Cluster randomised controlled trial; DUP: Duration of untreated psychosis; GP: General practitioner; LP: Liaison practitioner; MHRN: Mental health research network; MRC: Medical research council; PCRN EoE: Primary care research network east of England; TPB: Theory of planned behaviour; UHR: Ultra-high risk for psychosis.

Competing interests

The authors have no conflicts of interest based on business relationships of their own or of immediate family members.

Authors' contributions

PBJ is the chief investigator for this trial. JP and MP are principal investigator and project manager, respectively. All authors participated in the design of the study. DAR elaborated the theoretical basis of the project. JS and TJC were in charge of sample size calculations, statistical analysis and randomization. SB developed the EI-ADSUS questionnaire for economic evaluation. JZ participated in the design of the postal information campaign. JPG provided valuable advice with regards to implementation and support required in primary care. JP and DAR drafted the manuscript. All authors provided a critical review and approved the final manuscript.

Acknowledgements

The authors acknowledge funding support from the National Institute for Health Research (NIHR) programme grant RP-PG-0606-1335, Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses. TJC was supported by the Department of Health (DH)/NIHR career scientist award in public health. The work forms part of the NIHR Collaboration for Leadership in Applied Health Research and Care for Cambridgeshire and Peterborough (CLAHRC-CP). The authors also acknowledge the support offered by the PCRN EoE, the West Anglia CLRN and the East Anglia Hub of the MHRN. They thank the LEGS study team (Gill Shelley, Erica Jackson, Chris McAlinden and Carolyn Crane), and all members of CAMEO services for their help and support in the elaboration of this trial. The authors acknowledge support and advice from the late Professor Helen Lester in the conception of this trial.

Author details

[1]CAMEO Early Intervention Services, Cambridgeshire and Peterborough NHS Foundation Trust, Ida Darwin, Fulbourn, Block 7, Ida Darwin, Fulbourn, Cambridge CB21 5EE, UK. [2]Department of Psychiatry, Herchel Smith Building for Brain and Mind Sciences, University of Cambridge, Forvie Site, Robinson Way, Cambridge, UK. [3]Centre for the Economics of Mental and Physical Health, Institute of Psychiatry, King's College London, 16 De Crespigny Park, London SE5 8AF, UK. [4]Primary Care Unit, Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SR, UK. [5]Department of Health Sciences, Seebohm Rowntree Building, University of York, Heslington, York YO10 5DD, UK. [6]National Institute of Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care for Cambridgeshire and Peterborough (CLAHRC-CP), 18 Trumpington Road, Cambridge CB2 8AH, UK.

Received: 10 October 2012 Accepted: 3 July 2013
Published: 17 July 2013

References

1. Yung AR: **Commentary: the schizophrenia prodrome: a high-risk concept.** *Schizophr Bull* 2003, **29**(4):859–865.
2. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH: **Validity of the prodromal risk syndrome for first psychosis: findings from the north American prodrome longitudinal study.** *Schizophr Bull* 2009, **35**(5):894–908.
3. Platz C, Albrecht DS, Cattapan-Ludewig K, Dvorsky D, Arbach D, Brenner HD, Simon AE: **Help-seeking pathways in early psychosis.** *Soc Psychiatry Psychiatr Epidemiol* 2006, **41**:967–974.

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

4. Simon A, Lester HE, Tait L, Stip E, Roy P, Conrad G, Hunt J, Epstein I, Larsen T, Amminger P, Holub D, Wenigová B, Turner M, Berger G, O'Donnell C, Umbricht D: **The international study on general practitioners and early psychosis (IGPS).** *Schizophr Res* 2009, **108:**182–190.
5. Phillips LJ, Leicester SB, O'Dwyer LE, Francey SM, Koutsogiannis J, Abdel-Baki A, Kelly D, Jones S, Vay C, Yung AR, McGorry PD: **The PACE Clinic: identification and management of young people at "ultra" high risk of psychosis.** *J Psychiatr Pract* 2002, **8**(5):255–269.
6. Hegelstad WT, Larsen TK, Auestad B, Evensen J, Haahr U, Joa I, Johannesen JO, Langeveld J, Melle I, Opjordsmoen S, Rossberg JI, Rund BR, Simonsen E, Sundet K, Vaglum P, Friis S, McGlashan T: **Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome.** *Am J Psychiatry* 2012, **169**(4):374–380.
7. Gilbody S, Whitty P, Grimshaw J, Thomas R: **Educational and organisational interventions to improve the management of depression in primary care: a systematic review.** *JAMA* 2003, **289:**3145–3151.
8. Lester HE, Birchwood M, Freemantle N, Michail M, Tait L: **REDIRECT: cluster randomised controlled trial of GP training in first-episode psychosis.** *Br J Gen Pract* 2009, **59:**183–190.
9. Medical Research Council: *Developing and Evaluating Complex Interventions: New Guidance.* London: Medical Research Council; 2008.
10. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J: **Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states.** *Aust N Z J Psychiatry* 2005, **39**(11–12):964–971.
11. Crawford MJ, Killaspy H, Kalaitzaki E, Barrett B, Byford S, Patterson S, Soteriou T, ONeill FA, Clayton K, Maratos A, Barnes TR, Osborn D, Johnson T, King M, Tyrer P, Waller D: **The MATISSE study: a randomised trial of group art therapy for people with schizophrenia.** *BMC Psychiatry* 2010, **10:**65.
12. Flood C, Byford S, Henderson C, Leese M, Thornicroft G, Sutherby K, Szmukler G: **Joint crisis plans for people with psychosis: economic evaluation of a randomised controlled trial.** *BMJ* 2006, **333:**729.
13. McCrone P, Knapp M: **Economic evaluation of early intervention services.** *BJP* 2007, **191**(Suppl 51):19–22.
14. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB: **Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-centre AeSOP study.** *Arch Gen Psychiatry* 2006, **63**(3):250–258.
15. Curtis L: *Unit Costs of Health and Social Care 2012.* Kent: Personal Social Services Research Unit; 2012.
16. Joint Formulary Committee: *British National Formulary (BNF) 64.* London: BMJ Group and Pharmaceutical Press; 2012.
17. Department of Health: *NHS Reference Costs.* London: Department of Health; 2012.
18. Dubourg R, Hamed J: *The Economic and Social Costs of Crime against Individuals and Households 2003/04.* London: Home Office; 2005.
19. HM Prison Service: *Prison Service Annual Report and Accounts.* London: The Stationery Office; 2012.
20. Koopmanschap MA, Rutten F: **A practical guide for calculating indirect costs of disease.** *Pharmacoeconomics* 1996, **10:**460–466.
21. Barber JA, Thompson SG: **Analysis and interpretation of cost data in randomised controlled trials: review of published studies.** *BMJ* 1998, **317:**1195–1200.
22. Efron B, Tibshirani RJ: *An Introduction to the Bootstrap.* New York: Chapman & Hall; 1993.
23. Stinnett AA, Mullahy J: **Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis.** *Med Decis Making* 1998, **18:**S68–S80.
24. Gomes M, Ng ES, Grieve R, Nixon R, Carpenter J, Thompson S: **Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials.** *Med Decis Making* 2012, **32:**350–361.
25. Grieve R, Nixon R, Thompson SG, Normand C: **Using multilevelmodels for assessing the variability of multinational resource use and cost data.** *Health Economics* 2005, **14:**185–196.
26. Fenwick E, Byford S: **A guide to cost-effectiveness acceptability curves.** *Br J Psychiatry* 2005, **187:**106–108.
27. Phillips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riesmsa R, Woolacoot N, Glanville J: **Review of guidelines for good practice in decision-analytic modelling in health technology assessment.** *Health Technol Assess* 2004, **8**(36):1–158.
28. Coyle D, Lee KM: **Evidence-based economic evaluation: how the use of different data sources can impact results.** In *Evidence-based Health Economics.* Edited by Donaldson C, Mugford M, Vale L. London: BMJ Books; 2002:55–66.
29. Barton P, Bryan S, Robinson S: **Modelling in the economic evaluation of health care: selecting the appropriate approach.** *J Health Serv Res Policy* 2004, **9**(2):110–828.
30. Michie S, Johnston M: **Changing clinical behaviour by making guidelines specific.** *BMJ* 2004, **328:**343–345.
31. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR: **Why don't physicians follow clinical practice guidelines? A framework for improvement.** *JAMA* 1999, **282**(15):1458–1465.
32. Howe A, Ashton K, Hooper L: **Effectiveness of educational interventions in primary care mental health: a qualitative systematic review.** *Primary Care Comm Psychiatr* 2006, **11**(4):167–177.
33. Hodges B, Inch C, Silver I: **Improving the psychiatric knowledge, skills, and attitudes of primary care physicians, 1950–2000: a review.** *Am J Psychiatry* 2001, **158**(10):1579–1586.
34. Robertson R, Jochelson K: *Interventions that Change Clinician Behavior: Mapping the Literature.* London: National Institute for Health and Care Excellence; 2006.
35. Lester HE, Tait L, Keera A, Birchwood M, Freemantle N, Patterson P: **The development and implementation of an educational intervention on first episode psychosis for primary care.** *Med Ed* 2005, **39:**1006–1014.
36. Craik FIM, Lockhart RS: **Levels of processing: a framework for memory research.** *J Verb Learn Verb Beh* 1972, **11:**671–684.
37. Goering M, Wilson W: **Implementing preterm labour guidelines: a collaborative care improvement process.** *J Perinat Neonatal Nurs* 2002, **16**(1):47–57.
38. Foy R, Francis JJ, Johnston M, Eccles M, Lecouturier J, Bamford C, Grimshaw J: **The development of a theory-based intervention to promote appropriate disclosure of a diagnosis of dementia.** *BMC Health Serv Res* 2007, **7:**207.
39. Hrisos S, Eccles M, Johnston M, Francis J, Kaner EFS, Steen N, Grimshaw J: **Developing the content of two behavioural interventions: using theory-based interventions to promote GP management of upper respiratory tract infection without prescribing antibiotics #1.** *BMC Health Serv Res* 2008, **8:**11.
40. Eccles MP, Hrisos S, Francis J, Kaner EF, Dickinson HO, Beyer F, Johnston M: **Do self- reported intentions predict clinicians' behaviour: a systematic review.** *Implement Sci* 2006, **1**(28):10.
41. Bonetti D, Eccles M, Johnston M, Steen IN, Grimshaw J, Baker R, Walker A, Pitts N: **Guiding the design and selection of interventions to influence the implementation of evidence-based practice: an experimental simulation of a complex intervention trial.** *Soc Sci Med* 2005, **60:**2135–2147.
42. Michie S, Pilling S, Garety P, Whitty P, Eccles MP, Johnston M, Simmons J: **Difficulties implementing a mental health guideline: an exploratory investigation using psychological theory.** *Implement Sci* 2007, **2:**8.
43. Ajzen I: **From intentions to action: a theory of planned behavior.** In *Action Control: From Cognitions to Behaviors.* Edited by Kuhl J, Beckman J. New York: Springer; 1985:11–39.
44. Ajzen I: **The theory of planned behavior.** *Org Behavior Human Decision Proc* 1991, **50:**179–211.
45. Walker A, Watson M, Grimshaw J, Bond C: **Applying the theory of planned behaviour to pharmacists' beliefs and intentions about the treatment of vaginal candidiasis with non-prescription medicines.** *Fam Pract* 2004, **21:**670–676.
46. Ramsay CR, Thomas RE, Croal BL, Grimshaw JM, Eccles MP: **Using the theory of planned behaviour as a process evaluation tool in randomised trials of knowledge translation strategies: a case study from UK primary care.** *Implement Sci* 2010, **5:**71.
47. Green H, Johnston O, Cabrini S, Fornai G, Kendrick T: **General practitioner attitudes towards referral of eating-disordered patients: a vignette study based on the theory of planned behaviour.** *Ment Health Fam Med* 2008, **5**(4):213–218.
48. Ajzen I: *Constructing a TpB Questionnaire: Conceptual and Methodological Considerations.* Boston: UMASS; 2006.
49. Francis JJ, Eccles MP, Johnston M, Walker A, Grimshaw J, Foy R, Kaner EFS, Smith L, Bonetti D: *Constructing Questionnaires Based on the Theory of Planned Behaviour. A Manual for Health Services Researchers.* Newcastle upon Tyne: Centre for Health Services Research; 2004.

50. Russo DA, Stochl J, Croudace TJ, Graffy JP, Youens J, Jones PB, Perez J: **Use of the theory of planned behaviour to assess factors influencing the identification of individuals at ultra-high risk for psychosis in primary care.** *Early Interv Psychiatry* 2012, **6:**265–275.
51. Fife-Schaw CR, Sheeran P, Norman P: **Simulating behaviour change interventions based on the theory of planned behavior: impacts on intention and action.** *BJSP* 2007, **46:**43–68.
52. Abraham C, Michie S: **A taxonomy of behaviour change techniques used in interventions.** *Health Psychol* 2008, **27:**379–387.
53. Michie S, Johnston M, Francis J, Hardeman W, Eccles M: **From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques.** *Appl Psychol Int Rev* 2008, **57:**660–680.
54. Kitson A, Harvey G, McCormack B: **Enabling the implementation of evidence-based practice: a conceptual framework.** *Qual Health Care* 1998, **7:**149–158.
55. Bauchner H, Simpson L, Chessare J: **Changing physician behaviour.** *Arch Dis Childhood* 2001, **84:**459–462.
56. Wensing M, Grol R: **Multifaceted interventions.** In *Improving Patient Care: The Implementation of Change in Clinical Practice.* Edited by Grol R, Wensing M, Eccles M. Edinburgh: Elsevier; 2005.
57. Richens Y, Rycroft-Malone J, Morrell C: **Getting guidelines into practice: a literature review.** *Nursing Standard* 2004, **18**(50):33–40.
58. Ajzen I: *Behavioural Interventions Based on the Theory of Planned Behaviour.* Boston: UMASS; 2009.
59. Sutton S: **Testing attitude-behaviour theories using non-experimental data: an examination of some hidden assumptions.** *ERSP* 2002, **13:**293–323.
60. Harvey G, Loftus-Hills A, Rycroft-Malone J, Titchen A, Kitson A, McCormack B, Seers K: **Getting evidence into practice: the role and function of facilitation.** *J Adv Nurs* 2002, **37**(6):577–588.
61. Alvanzo AH, Cohen GM, Nettleman M: **Changing physician behaviour: half-empty or half-full?** *Clin GovernInt J* 2003, **8**(1):69–78.
62. Bandura A: *Self-efficacy: The Exercise of Control.* New York: Freeman; 1997.
63. Pajares F: **Current directions in self-efficacy research.** In *Advances in Motivation and Achievement. Volume 10.* Edited by Maehr M, Pintrich PR. Bingley: Emerald Group Publishing Limited; 1997:1–49.
64. Hong SW, Ching TY, Fung JP, Seto WL: **The employment of ward opinion leaders for continuing education in the hospital.** *Medical Teacher* 1990, **12:**209–217.
65. Valente TW, Pumpuang P: **Identifying opinion leaders to promote behavior change.** *Health Educ Behav* 2007, **34:**881.
66. Power P, Iacoponi E, Reynolds N, Fisher H, Russell M, Garety P, McGuire P, Craig T: **The Lambeth early onset crisis assessment team study: general practitioner education and access to an early detection team in first-episode psychosis.** *Br J Psychiatry Suppl* 2007, **191**(Suppl 51):133–139.
67. Simon A, Jegerlehner S, Müller T, Cattapan-Ludewig K, Frey P, Grossenbacher M, Seifritz E, Umbricht D: **Early schizophrenia in primary care: a randomized sensitization study.** *BJGP* 2010, **60**(578):353–359.
68. Darker CD, French DP, Eves FF, Sniehotta FF: **An intervention to promote walking amongst the general population based on an 'extended' theory of planned behaviour: a waiting list randomised controlled trial.** *Psychol Health* 2010, **25:**71–88.

doi:10.1186/1745-6215-14-222
Cite this article as: Perez *et al.*: Comparison of high and low intensity contact between secondary and primary care to detect people at ultra-high risk for psychosis: study protocol for a theory-based, cluster randomized controlled trial. *Trials* 2013 **14**:222.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

© 2013 Perez *et al.*; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Appendix 7 Clinical effectiveness and cost-effectiveness of tailored intensive liaison between primary and secondary care to identify individuals at risk of a first psychotic illness (the LEGS study): a cluster-randomised controlled trial

Articles

Clinical effectiveness and cost-effectiveness of tailored intensive liaison between primary and secondary care to identify individuals at risk of a first psychotic illness (the LEGs study): a cluster-randomised controlled trial

Jesus Perez, Huajie Jin, Debra A Russo, Jan Stochl, Michelle Painter, Gill Shelley, Erica Jackson, Carolyn Crane, Jonathan P Graffy, Tim J Croudace, Sarah Byford, Peter B Jones

Lancet Psychiatry 2015; 2: 984–93

Published Online August 19, 2015 http://dx.doi.org/10.1016/S2215-0366(15)00157-1

See Comment page 951

CAMEO Early Intervention Services, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK (J Perez PhD, D A Russo BSc, J Stochl PhD, M Painter MPhil, G Shelley BA, E Jackson BA, C Crane MSc, Prof P B Jones PhD); **Department of Psychiatry** (J Perez, D A Russo, J Stochl, C Crane, Prof P B Jones) **and Primary Care Unit, Department of Public Health and Primary Care** (J P Graffy MD), **University of Cambridge, Cambridge, UK; Centre for the Economics of Mental and Physical Health, King's College London, London, UK** (H Jin MSc, Prof S Byford PhD); **Department of Kinanthropology, Charles University, Prague, Czech Republic** (J Stochl); **School of Nursing and Midwifery, Social Dimensions of Health Institute, University of Dundee, Dundee, Scotland** (Prof T J Croudace PhD); **and National Institute of Health Research Collaboration for Leadership in Applied Health Research and Care East of England (CLAHRC-EoE), Cambridge, UK** (J Perez, J Stochl, Prof P B Jones)

Correspondence to Prof Peter B Jones, Department of Psychiatry, University of Cambridge, Herchel Smith Building, Cambridge CB2 0SZ, UK **pbj21@cam.ac.uk**

Summary

Background General practitioners are usually the first health professionals to be contacted by people with early signs of psychosis. We aimed to assess whether increased liaison between primary and secondary care improves the clinical effectiveness and cost-effectiveness of detection of people with, or at high risk of developing, a first psychotic illness.

Methods Our Liaison and Education in General Practices (LEGs) study was a cluster-randomised controlled trial of primary care practices (clusters) in Cambridgeshire and Peterborough, UK. Consenting practices were randomly allocated (1:1) to a 2 year low-intensity intervention (a postal campaign, consisting of biannual guidelines to help identify and refer individuals with early signs of psychosis) or a high-intensity intervention, which additionally included a specialist mental health professional who liaised with every practice and a theory-based educational package. Practices were not masked to group allocation. Practices that did not consent to be randomly assigned comprised a practice-as-usual (PAU) group. The primary outcome was number of referrals of patients at high risk of developing psychosis to the early intervention service per practice site. New referrals were assessed clinically and stratified into those who met criteria for high risk or first-episode psychotic illness (FEP; together: psychosis true positives), and those who did not fulfil such criteria for psychosis (false positives). Referrals from PAU practices were also analysed. We assessed cost-effectiveness with decision analytic modelling in terms of the incremental cost per additional true positive identified. The trial is registered at the ISRCTN registry, number ISRCTN70185866.

Findings Between Dec 22, 2009, and Sept 7, 2010, 54 of 104 eligible practices provided consent and between Feb 16, 2010, and Feb 11, 2011, these practices were randomly allocated to interventions (28 to low intensity and 26 to high intensity); the remaining 50 practices comprised the PAU group. Two high-intensity practices were excluded from the analysis. In the 2 year intervention period, high-intensity practices referred more FEP cases than did low-intensity practices (mean 1·25 [SD 1·2] for high intensity *vs* 0·7 [0·9] for low intensity; incidence rate ratio [IRR] 1·9, 95% CI 1·05–3·4, p=0·04), although the difference was not statistically significant for individuals at high risk of psychosis (0·9 [1·0] *vs* 0·5 [1·0]; 2·2, 0·9–5·1, p=0·08). For high risk and FEP combined, high-intensity practices referred both more true-positive (2·2 [1·7] *vs* 1·1 [1·7]; 2·0, 1·1–3·6, p=0·02) and false-positive (2·3 [2·4] *vs* 0·9 [1·2]; 2·6, 1·3–5·0, p=0·005) cases. Referral patterns did not differ between low-intensity and PAU practices. Total cost per true-positive referral in the 2 year follow-up was £26 785 in high-intensity practices, £27 840 in low-intensity practices, and £30 007 in PAU practices.

Interpretation This intensive intervention to improve liaison between primary and secondary care for people with early signs of psychosis was clinically and cost effective.

Funding UK National Institute for Health Research.

Copyright © Perez et al. Open Access article distributed under the terms of CC BY.

Introduction

A first episode of psychotic illness (FEP) can be devastating. Usually the illness first occurs in adolescence or early adulthood, puncturing a phase of rapid personal and social development. Some people with this disorder recover completely, but most never return to their personal developmental trajectory; others will have repeated episodes and long-term disability. Worldwide, clinical practice is increasingly predicated on early intervention, often by specialist teams in secondary care relying predominantly on patient referrals from primary care. In the past 5 years, early intervention services have come under budgetary pressures, despite strong health-economic evidence showing that prompt specialist care promotes patient recovery and is a cost-effective method.[1] However, no evidence has yet shown that improved detection of FEP by early identification of individuals at high risk of developing psychosis might also be a cost-effective method to reduce the duration of undetected and untreated illness.

© Perez *et al.* Open Access article distributed under the terms of CC BY.

Research in context

Systematic review

We searched for studies that attempted exclusively to educate general practitioners (GPs) to recognise people at high risk of developing psychosis or those with their first episode of psychotic illness, with the aim of increasing referral of patients to specialist services. We searched PsycInfo, MEDLINE, Embase, British Nursing Index, CINAHL, HMIC, and the Social Science Citation Index using the terms "early intervention", "psychosis" (psychotic symptoms, psychotic disorder, psychotic illness, schizophrenia), "risk" (at-risk-mental-state, prodrome, high-risk, psychotic-like), "GPs", "primary care", "education", and "health services", from Jan 1, 2001, onwards (because in this year the high risk concept was widely used and implementation of early intervention services commenced across the UK). Thesaurus and free-text terms were combined. Our search identified only two randomised controlled trials (REDIRECT[8] and LEO CAT[7]) and two naturalistic studies.[28,29] The REDIRECT trial[8] showed that training of GPs was insufficient to alter FEP referral rates to early intervention services, although access to specialist teams was accelerated by the intervention. By contrast, the LEO CAT trial,[7] which combined training of GPs and patient access to a specialist service, significantly increased referral of patients with FEP to mental health services and reduced delays in treatment provision. Simon and colleagues[28] found that increasing GPs' awareness of high-risk symptoms resulted in a significant increase in diagnostic knowledge. However, the study did not evaluate whether this resulted in more accurate or increased referrals to secondary care services. Reynolds and colleagues[29] assessed the effect of GP training on high-risk referrals and concluded that the intervention significantly increased direct referrals to specialist teams.

Interpretation

Few studies, with disparate results, have attempted to educate GPs to recognise individuals at high risk of developing psychosis or those with FEP to improve patient access to secondary mental health services. None of the studies used a theory-based framework or considered the economic effects of different interventions with a randomised study design. Our cluster-randomised controlled trial shows that additional expenditure, by use of tailored intensive liaison between primary and secondary care to identify and help with the referral of individuals with early signs of psychosis, adds clinical and economic value.

General practitioners (GPs; primary care physicians) are usually the first health professionals contacted by individuals at high risk of developing psychosis.[2] Early detection of psychosis in primary care is difficult because of the non-specific nature of its behavioural and psychological antecedents and the very low predictive value for this rare outcome.[3] Some early intervention services in Scandinavia and Australia have developed protocols for the detection of people at high risk in primary care.[4,5] No study has assessed the clinical effectiveness and cost-effectiveness of different approaches, despite evidence that the education of GPs alone does not improve the management and identification of mental health disorders in primary care.[6]

Two previous randomised controlled trials focused on education of GPs to recognise patients with FEP.[7,8] The LEO CAT study[7] randomly assigned an intervention that combined GP education and direct patient access to a specialist service and compared this with routine access to generic services. The intervention significantly increased the number of prompt referrals of patients with FEP to mental health services.[7] By contrast, the REDIRECT trial[8] showed that training of GPs alone was insufficient to alter referral rates of patients with FEP to early intervention services, although access to specialist teams was accelerated by the intervention. Neither study considered patients at high risk of developing psychosis, used a theory-based framework derived from educational research to help understand what might work to change behaviour of GPs, or assessed the economic effects of different interventions to change referral patterns.

We aimed to compare two different approaches to liaison between primary care and specialist secondary care—early intervention services for detection and early referral of young people at high risk of developing psychosis. We tested the null hypothesis that a high-intensity, theory-based, ongoing educational intervention for primary care—including liaison through named, specialist health professionals allocated to practices—is not different, in terms of clinical effectiveness and cost-effectiveness, to the provision of referral guidelines sent by post, together with ad hoc clinical contacts stemming from routine practice.

Our study is timely in view of the recent announcement from the UK Government[9] of patient waiting time targets being extended to mental health in general, and patients with FEP in particular, and the uncertainty in financially challenged services. We investigated whether increasing the resources aimed at managing the interface from primary care to secondary care increased detection of young people at high risk of developing psychosis and early referral to a specialist early intervention team.

Methods

Study design and participants

Our Liaison and Education in General Practices (LEGs) study was a cluster-randomised controlled trial of primary-care general practices (clusters) in the county of Cambridgeshire and city of Peterborough (both UK). It also included an economic assessment. The protocol has been published elsewhere.[10] Consenting primary-care practices were randomly assigned to either a high-intensity

Articles

or low-intensity approach to liaison between primary care and a specialist early intervention service for psychosis (secondary care). Practices that did not consent to randomisation formed a practice-as-usual (PAU) group. Written consent was obtained from the lead GP at every practice. Our approach and methodology followed the Medical Research Council (MRC) guidelines for the design and assessment of complex interventions.[11]

104 general practices, working across 138 surgeries (some practices operated from more than one surgery with shared clinical staff), in Cambridgeshire and Peterborough were identified from the Primary Care Research Network (PCRN) East of England (now CRN Eastern Primary Care) database. Cambridgeshire and Peterborough have a total population of about 825 000 people who live in diverse socioeconomic settings—including in urban, suburban, and rural communities. In the 2011 census,[12] 38% of this population lived in electoral wards classified with above-average levels of the English Multiple Deprivation Index.

For the **CRN Eastern Primary Care** see http://www.crn.nihr.ac.uk/eastern/

Routine data were available for the number of high risk and FEP referrals from all practices, including those that did not consent to be randomly assigned to an intervention. These data allowed assessment of the generalisability and validity of our findings.[10]

All participating practices referred patients to an established, county-wide early intervention service for the management of FEP (CAMEO). The Cambridgeshire East Research Ethics Committee, Cambridge, UK, approved the study (reference 09/H0304/46). We only counted data for referrals of patients aged 16–35 years. We used no other exclusion criteria.

For more about **CAMEO** see http://www.cameo.nhs.uk

Randomisation and masking

Practices randomly assigned to treatment groups were stratified according to three high-level factors considered a priori to be likely to be associated with referral behaviour: three geographical areas representative of the socioeconomic status in the UK (Cambridge and south Cambridgeshire [highest], Huntingdon and east Cambridgeshire, and Peterborough and Fenland [lowest]); whether GPs worked at several sites (yes *vs* no); and membership of Association of Student Practices in Cambridge (yes *vs* no), of which university students account for a high proportion (about 50%) of total list sizes.

After practices provided their consent, TJC randomly assigned practices with a computer-generated permuted sequence in blocks with 12 strata and 96 blocks, independently from the research team members who were not told of the process. This computer sequence was generated by the RALLOC command in Stata (version 11.0).[13] Several steps were taken to keep those involved at various stages of the trial masked to the intervention groups. General practices could not be masked because the difference between the interventions was described in the information sheet required by the Cambridgeshire ethics committee. Practices randomly assigned to the high-intensity intervention would have discerned their allocation when they were contacted to arrange an educational session for the GPs. Liaison practitioners who enrolled participants and delivered the intervention could not be masked, because they had to know what intervention to deliver (eg, the high-intensity intervention). However, all patient referrals were received through a central point of contact; the administrator (part of the research team) responsible for this process was masked to the intervention allocation. All referrals were assessed by senior research clinicians who were masked to the practice allocation to an intervention. This masking process could be compromised through contact with treating clinicians but knowledge of referral origin was reduced by accommodating researchers in a different part of the building from the clinical team. Additionally, these clinicians took part in inter-rater reliability meetings once per week that were held to determine whether every referral was at high risk of developing psychosis, had FEP, or did not have psychosis. Everyone involved in this process was masked to practice origin, providing assurance that referrals from the three practice groups (high intensity, low intensity, PAU) were not being assessed differently and that raters were concordant. The trial statistician (JS) was not masked to practice allocation, but analysed only the count data provided.

See Online for appendix

Procedures

Practices were provided consent to participate between Dec 22, 2009, and Sept 7, 2010. Referral activity by primary-care practices and the results of specialist clinical assessments were recorded for 2 years after random allocation to an intervention group between Feb 16, 2010, and Feb 11, 2011.

The Comprehensive Assessment of At-Risk Mental States (CAARMS) interviews, semistructured and designed to detect prodromal symptoms of psychotic disorders to suggest which patients are at high risk of transition to FEP, were done by senior research clinicians trained by experts involved in previous trials that used it, such as the MRC EDIE trial.[14] CAARMS is also used to determine whether an individual meets criteria for high risk or FEP. It is divided into four main symptom domains: unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech. This interview system's scores include intensity and frequency of these symptoms, and has good-to-excellent concurrent, discriminatory, and predictive validity in this setting and excellent inter-rater reliability.[15] Inter-rater reliability was based on 104 evaluations by three independent raters and showed an excellent overall agreement for all four CAARMS domain scores (intra-class correlation mean 0·98; SD 0·1; range 0·96–1).

The main element of the low-intensity intervention was a postal information campaign, comprising a specifically designed laminated leaflet (appendix). The leaflet provided guidelines to help GPs identify and refer

© Perez *et al.* Open Access article distributed under the terms of CC BY.

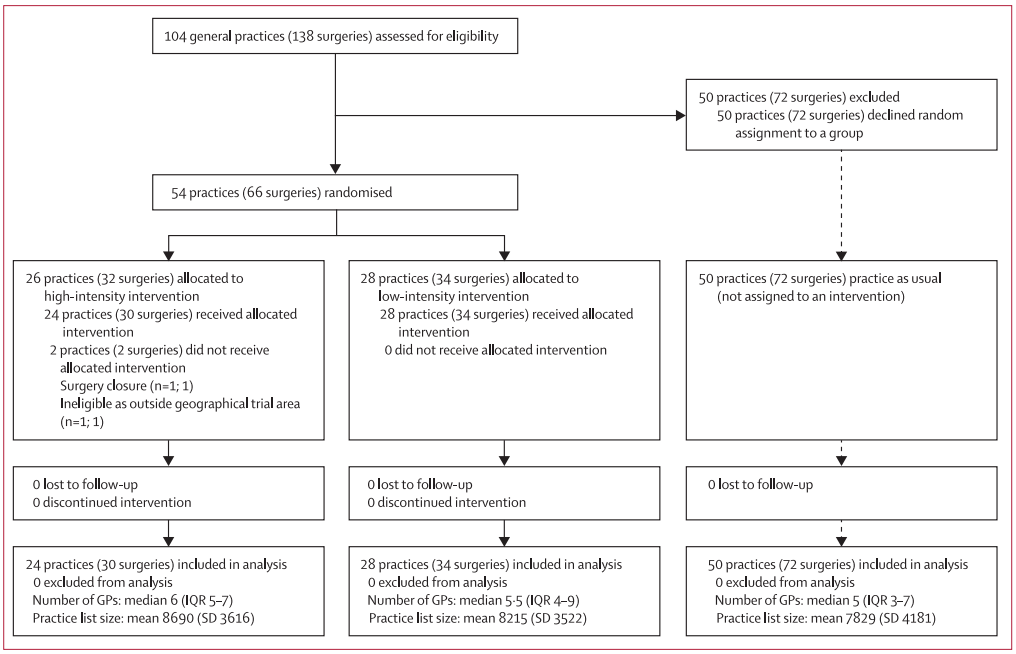


Figure 1: **Trial profile**
GPs=general practitioners.

individuals at high risk or those with FEP. It was posted to the practices in the low-intensity group every 6 months during the study. The leaflets were integrated within the high-intensity educational programme (high-intensity intervention) and distributed at the same frequency as low intensity to compare the two groups.[10]

The high-intensity intervention comprised a tailored education and liaison approach between primary and secondary care, designed using the principles of the MRC framework for the development and evaluation of complex interventions[11] and evidence about effective educational interventions in primary mental health care.[16] We addressed the absence of an explicit theoretical framework in the design of many educational interventions to change professional practice[17] by using the Theory of Planned Behaviour (TPB),[18,19] which predicts intentions and behaviour in relation to clinical practice.[20] This theory proposes that the identification of individuals at high risk of developing psychosis in primary care is predicted by the strength of a GP's intention to identify these individuals. This intention is affected by three predictor variables: whether the GP is in favour of identification (attitude); the intensity of social pressure the GP perceives to identify early psychosis (subjective norm); and how much the GP feels in control of this identification process (perceived behavioural control).[19]

Use of the TPB to design interventions requires the development of a questionnaire to allow the identification and measurement of specific beliefs associated with each construct (ie, intention, attitude, subjective norm, and perceived behavioural control). In accordance with the TPB guidelines,[21,22] pilot work was undertaken before this study to identify accessible behavioural, normative, and control beliefs. This work generated a questionnaire that was used to measure factors that affected a GP's identification of individuals at high risk of developing psychosis. The pilot work also guided the development of the materials and strategies included in the intervention, which were aimed at encouraging GPs to identify individuals at high risk by incorporating apposite knowledge and skills into their practice.[23]

These techniques were delivered and facilitated by three liaison practitioners over the 2 year intervention period. All three practitioners were experienced mental health professionals responsible for delivering the intervention to the consenting practices within one of the three chosen geographical areas in Cambridgeshire. The main behavioural change technique consisted of two practice-based educational sessions. An initial 1 h educational session was on detection of high-risk individuals for practices when they started the trial and was followed 1 year later by a booster 1 h session to reiterate the main messages, consolidate skills and knowledge, discuss particular practical scenarios that emerged during the course of the study, and to adjust or improve ongoing intensive liaison techniques if needed.

	High intensity (n=24)	Low intensity (n=28)	Practice as usual (n=50)	p value
Number of GPs	6 (5–7)	5·5 (4–9)	5 (3–7)	NA
Practice patient list size	8690 (3616)	8215 (3522)	7829 (4181)	0·66*; 0·17†‡
Number of additional sites	0 (0–0)	0 (0–0)	0 (0–1)	NA
University affiliated surgery				0·09§; 0·06¶; 0·07†§; 0·06†¶
Yes	3 (13%)	4 (14%)	1 (2%)	
No	21 (88%)	24 (86%)	49 (98%)	
Number of GPs working across several sites				0·25§; 0·29¶; 0·15†§; 0·13†¶
Yes	6 (25%)	6 (21%)	19 (38%)	
No	18 (75%)	22 (79%)	31 (62%)	
Practices per region				0·58§; 0·57¶; 0·26†§; 0·27†¶
Huntingdon and east Cambridgeshire	8 (33%)	10 (36%)	12 (24%)	
Peterborough and Fenland	7 (29%)	9 (32%)	23 (46%)	
South Cambridgeshire	9 (38%)	9 (32%)	15 (30%)	

Data are median (IQR), mean (SD), or n (%), unless otherwise stated. GPs=general practitioners. *F test. †Statistical differences between practices that consented (high intensity plus low intensity) and did not consent (practice as usual) to be randomly assigned. ‡Kruskal-Wallis χ^2 test. §Pearson's χ^2 test. ¶Fisher's exact test.

Table 1: **Baseline characteristics of high-intensity, low-intensity, and practice-as-usual general practices**

This approach allowed the intervention to be tailored to meet the specific needs of every practice. Together with other components of the intervention, this allowed comparisons of cost-effectiveness between the resource intensive strategy (high-intensity intervention) and simple postal information campaign (low-intensity intervention).[10]

Practices that did not consent to be randomly assigned between the two interventions continued to receive postal leaflet information about early signs of psychosis, but without a specific focus on patients at high risk and did not receive the leaflet as often as the low-intensity campaign (PAU: once per year *vs* low-intensity and high-intensity: twice per year).

Outcomes

The primary outcome was count data (ie, number) of high-risk referrals to the early intervention service analysed per practice (the yield) during the 2 years of this study. New patient referrals during the trial who were clinically assessed by the study team were stratified into those who met criteria for high risk or FEP according to CAARMS[15] (psychosis true positives) and those who did not fulfil the criteria (false positives). Additionally, the economic evaluation assessed the cost-effectiveness of both interventions in terms of detection of true-positive patients (at high risk or with FEP).

Statistical analysis

We used sample size formulae for Poisson outcomes in a cluster-randomised controlled trial design, comparing high-intensity and low-intensity interventions, and an assumption that the high-intensity intervention would double the number of referrals of patients at high risk of developing psychosis to secondary care compared with the low-intensity intervention. For power of 80% with a significance level at 0·05 (two-sided), referral counts expressed as an incidence rate of referrals in the low-intensity group of 40 per 100 000 person-years,[24] an anticipated incidence rate in the high-intensity group of 80 per 100 000 person-years, 2000 person-years per site (average surgery list size for patients aged 16–35 years per 2 years of study), and a coefficient of variation estimated at 0·15, our calculations showed we needed a sample size of 31 surgeries (sites) in each arm.

The main outcome was count data, the yield, so our primary statistical approach was Poisson regression. If the assumptions of Poisson regression were not met (eg, over-dispersion), we used alternative models such as quasi-Poisson, Poisson with robust standard errors, or negative binomial regression models. If excessive numbers of zeros were noted, we then used zero inflated models and hurdle models. The fit of the model to the data was assessed by comparison of model log-likelihoods (between Poisson and negative binomial model) or the Vuong test[25] (between Poisson and zero inflated model). Subsequently, the best fitting model was selected, although the overall pattern of results showed no difference between models. Analysis was by modified intention to treat. All practices were considered to remain in their allocated groups irrespective of subsequent engagement in the trial interventions and other matters, unless practices closed, withdrew, or became ineligible from the study immediately after randomisation.

Results were adjusted for surgery size, regarding the number of GPs working in each site as an offset variable in the model. As our main predictors (low intensity, high intensity, or PAU) were categorical variables, we first set the high-intensity group as the reference. However, this choice did not allow for direct comparisons between the low-intensity and PAU groups so, in this case, we then used the low-intensity group as the reference. We also used F tests, Kruskal-Wallis χ^2 test, Pearson's χ^2 test, and Fisher's exact test to compare demographic characteristics of the general practices. For inter-rater reliability of CAARMS, we used intraclass correlation coefficient.[26] A sensitivity analysis assessed the effect of some individuals refusing assessment after referral. All analyses were done using the statistical package R version 3.1.2.[27]

Economic analysis

The economic evaluation aimed to explore the cost-effectiveness of the high-intensity and low-intensity interventions compared with the PAU group, using decision analytical modelling. We constructed a decision tree in Excel 2013 to model the care pathways of the young people in the trial and to assess the costs and effects in 2 years associated with the two active interventions and PAU. Costs chosen in the analysis were those relevant to

© Perez *et al.* Open Access article distributed under the terms of CC BY.

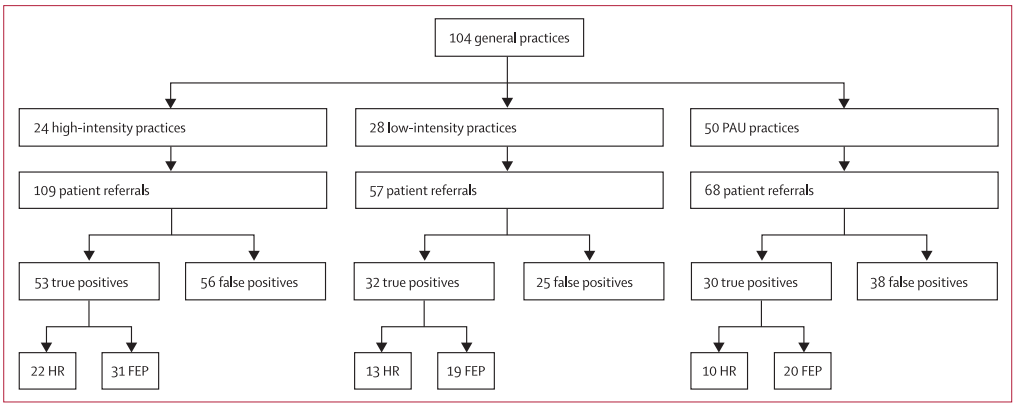


Figure 2: **Number and type of referrals by general practices in Cambridgeshire and Peterborough**
PAU=practice as usual. HR=high risk of developing psychosis. FEP=first-episode of psychotic illness.

the UK's National Health Service (NHS) and social care in England and included costs of the high-intensity and low-intensity interventions, diagnosis of referrals who did not meet criteria for high risk or FEP (false positives), diagnosis and treatment of patients identified as high risk and FEP (true positives), and the subsequent treatment for high risk and FEP who were not identified (false negatives). The cost of true-negative cases was assumed to be zero.

Cost-effectiveness was expressed as the incremental cost per additional true-positive case (high risk or FEP) identified. Input data were obtained mainly from this cluster-randomised controlled trial, with economic data gathered from a service use schedule designed for use with an early intervention sample. This schedule was completed by the individuals at high risk or with FEP who were referred to CAMEO and repeated at 6, 12, 18, and 24 months. Data for input parameters not available from the trial—eg, for patients at high risk or with FEP not identified in the study (false negatives)—were estimated using published data (appendix). Full details about the economic methods are provided in the appendix.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. JP, HJ, DAR, JS, SB, and PBJ had full access to the raw data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of the 104 general practices (138 surgeries) in Cambridgeshire and Peterborough eligible to participate, 54 practices (66 surgeries) consented to be randomly assigned between Dec 22, 2009, and Sept 7, 2010. 28 practices (34 surgeries) were assigned to the low-intensity group and 26 practices (32 surgeries) to the high-intensity group (figure 1). In the high-intensity group, two practices (two surgeries) were excluded because one practice closed soon after consenting and its patients dispersed to other practices in the study, and the other was incorrectly on the list of eligible practices because it was outside the county and catchment area of the early intervention service. 50 practices (72 surgeries) did not consent to randomisation and thus formed the PAU group (figure 1). 34 (68%) of these practices provided no reason

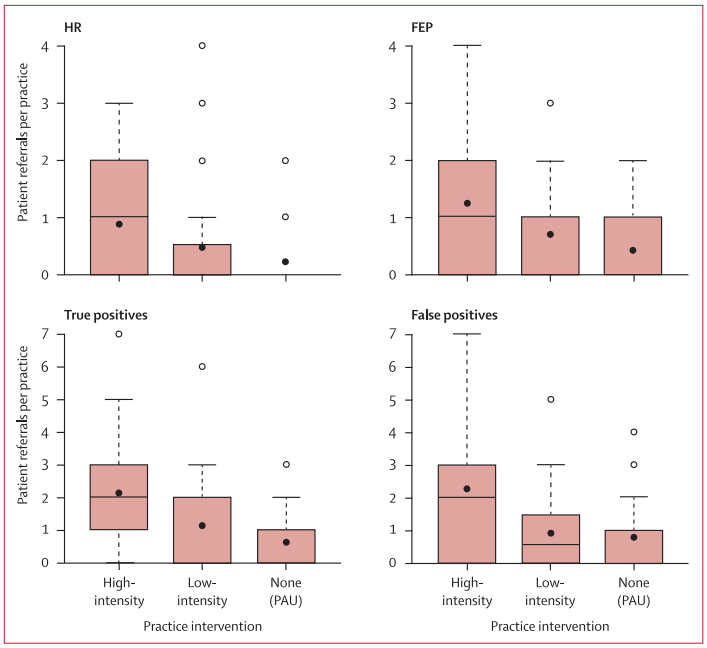


Figure 3: **Box plot of the distribution of patient referrals from primary care to secondary care**
HR=high risk of developing psychosis. FEP=first episode of psychotic illness. PAU=practice as usual. Lower bounds show the 25th percentile. Upper bounds show the 75th percentile. Line represents the median. Black dot represents the mean. White dots show the outliers.

	High risk of developing psychosis*	First episode of psychotic illness†	True positives*	False positives*
Reference: low intensity				
Intercept	0·1 (0·03–0·2); p<0·0001	0·1 (0·07–0·2); p <0·0001	0·2 (0·1–0·3); p <0·0001	0·1 (0·09–0·2); p <0·0001
High *vs* low	2·2 (0·9–5·1); p=0·08	1·9 (1·05–3·4); p=0·04	2·0 (1·1–3·5); p=0·02	2·6 (1·3–5·0); p=0·005
PAU *vs* low	0·5 (0·2–1·5); p=0·2	0·7 (0·4–1·3); p=0·2	0·6 (0·3–1·2); p=0·1	1·0 (0·5–1·9); p=1·0
Reference: high intensity				
Intercept	0·2 (0·1–0·2); p<0·0001	0·2 (0·1–0·3); p<0·0001	0·4 (0·3–0·5); p<0·0001	0·4 (0·3–0·6); p<0·0001
Low *vs* high	0·5 (0·2–1·1); p=0·08	0·5 (0·3–0·9); p=0·035	0·5 (0·3–0·9); p=0·017	0·4 (0·2–0·8); p=0·005
PAU *vs* high	0·3 (0·1–0·6); p<0·0001	0·4 (0·2–0·6); p<0·0001	0·3 (0·2–0·5); p<0·0001	0·4 (0·2–0·7); p<0·0001

Data are incidence rate ratios (95% CI), unless otherwise stated. *Negative binomial test. †Poisson test.

Table 2: **Comparison of effectiveness (incidence rate ratios) between high-intensity, low-intensity, and practice-as-usual (PAU) general practices**

for not consenting, 14 (28%) attributed their decision to high workload, and two (4%) to a large number of ongoing research projects. No PAU practice had a specific alternative approach for liaison with secondary care.

Table 1 shows baseline characteristics of practices in the high-intensity, low-intensity, and PAU groups; we did not note any significant differences between groups. During the 2 year intervention period, 234 patient referrals were made to the specialist early intervention in psychosis service (CAMEO) from the study practices for assessment of possible psychotic symptom (figure 2). The mean number of referrals during the 2 years from the high-intensity group was 4·5 per practice (SD 3·1), 2·0 (2·55) from the low-intensity group, and 1·4 (1·5) from the PAU group.

39 (17%) referrals received during the 2-year intervention were not included in the analysis because the individuals declined clinical assessment; therefore, their clinical status could not be ascertained. 16 (41%) patients were referred by high-intensity practices, seven (18%) patients by low-intensity practices, and 16 (41%) patient referrals were made by practices in the PAU group.

In terms of mean numbers of referrals per practice (figure 3), high-intensity practices referred more people who were subsequently identified to be at high risk (0·9 [SD 1·0]) or with FEP (1·25 [1·2]; combined as psychosis true positives) than did low-intensity practices (high risk 0·5 [1·0]; FEP 0·7 [0·9]) and PAU general practices (high risk 0·2 [1·5]; FEP 0·4 [0·6]). The high-intensity practices referred the most true-positive cases (patients at high risk or who had FEP; 2·2 [1·7]; low intensity 1·1 [1·7]; PAU 0·6 [0·85]). The same pattern was noted for referrals of false positives (patients not at high risk or who did not have FEP; high-intensity practices 2·3 [SD 2·4], low-intensity practices 0·9 [1·2], and PAU 0·8 [1·1]). However, 81 (68%) of individuals without psychosis (false positive) who were diagnosed in this trial were directed to other mental-health-related services for help with their problems; 23 (28%) needed input from secondary or tertiary mental health services. 58 (72%) individuals were referred to Improved Access to Psychological Therapies (IAPT) services in primary care, wherein they would receive up to 20 sessions of largely cognitive behavioural therapies.

For more about **IAPT** see http://www.iapt.nhs.uk

	Mean number of true-positive cases identified per practice (SD)	Total 2-year cost per practice
High intensity	2·2 (1·7)	£26 785
Low intensity	1·1 (1·7)	£27 840
Practice as usual	0·6 (0·85)	£30 007

Table 3: **2-year costs and cases identified per general practice, by intervention group**

The best fitting model for every group of referrals was reported (table 2). High-intensity practices referred more FEP (incidence rate ratio [IRR] 1·9, 95% CI 1·05–3·4, p=0·04) and true-positive cases (2·0, 1·1–3·6, p=0·02) than did the low-intensity and PAU practices (table 2). High-intensity practices also referred the most false-positive cases (2·6, 1·3–5·0, p=0·005). The low-intensity postal campaign seemed to have very little effect on number of referrals compared with the PAU group. The number of referrals from high-intensity practices was higher than from PAU in all monitored referral groups (figure 2). Sensitivity analyses, including the 39 patients who declined assessment, did not modify any of these results (further details about these analyses and the statistical model-building that led to these results are available from the authors).

Total costs and effect on the number of referrals per practice during the 2 year follow-up were compared between intervention groups (table 3). Compared with both the low-intensity intervention and PAU group, the high-intensity intervention was more effective at identifying patients at high risk of developing psychosis or with FEP and was associated with lower total costs per practice, mainly as a result of fewer false-negative cases (patients at high risk and FEP not identified, but who are assumed to be associated with later treatment costs; appendix). Thus, the high-intensity intervention was more cost effective than both the alternative liaison approaches. These results were robust to one-way and probabilistic sensitivity analyses (appendix; patient level data are available from the authors on request).

© Perez *et al.* Open Access article distributed under the terms of CC BY.

Discussion

Our cluster-randomised controlled trial showed that tailored and intensive liaison between primary and secondary care to detect people with early signs of psychosis and to help improve their access to mental health services can be clinically and cost effective. Our theory-based, high-intensity intervention was more effective than a postal information campaign at increasing number of referrals to specialist care for patients with FEP or at high risk of developing psychosis (panel). This intervention was costly both in terms of resources and time. However, the economic decision model suggests that this additional expenditure has the potential to generate subsequent savings through earlier detection and referral to specialist early intervention services.

Our work was informed by the LEO CAT study,[7] which assessed the effectiveness of educating GPs and provision of a specialist service to help with the identification of a FEP. However, important differences exist between our study and the LEO CAT study. First, we lowered the threshold for psychotic symptoms and attempted to educate GPs to also identify individuals at high risk. Second, our overall sample was larger and the trial covered a more diverse socioeconomic area (including urban, suburban, and rural settings) and an established early intervention service for psychosis. Third, we focused on the educational package. In the LEO CAT trial,[7] the intervention group also had direct access to the LEO CAT clinical team designed to work closely with GPs, whereas the control group received standard care provided by community mental health services. Therefore, it is not possible to determine if one or both of these elements resulted in the increased number of referrals in the LEO CAT study. Fourth, our educational intervention was developed using a theory-based framework derived from educational research. Despite the success of the intervention in the LEO CAT study,[7] it is difficult to identify which specific factors changed the referral behaviour in GPs. The absence of a theoretical framework underpinning interventions used in previous studies has obscured understanding of the behavioural determinants (what to target) and the selection of techniques to change these determinants (how to target them). As a result, such interventions are difficult to replicate, which precludes their development across different contexts and populations.[30] Finally, we included an economic analysis; if the intervention were to prove costly in terms of resources and time, the benefit of any number of increased referrals might be negated.

Our intervention doubled the number of referrals of patients at high risk, matching our prediction, but the confidence limit for this effect included unity, failing to reject the primary null-hypothesis. However, this effect was matched by almost twice the number of referrals of patients with FEP and false-positive cases so we believe it is likely to be true. Growing evidence suggests that psychosis represents a continuum, with psychosis proneness and mild psychotic symptoms at one end and schizophrenia and other psychotic disorders at the other.[31] Individuals in high-risk states and those with FEP in our trial sought help, and thus probably together represented the severe end of this psychosis continuum rather than different categorical entities from each other.[32] Accordingly, we grouped individuals at high risk and those with FEP as psychosis true positives, showing the overall number of individuals seeking help. Their combined referral numbers were doubled by the high-intensity intervention. We believe that our high-intensity intervention enhanced the detection of individuals with psychotic symptoms in primary care and their referral to the early intervention service.

In our study, high-intensity practices also referred more people without psychosis (false positives) than did the low-intensity intervention or PAU practices. A possibility for this might be that the high-intensity intervention raised awareness and increased sensitivity in GPs' referral behaviour in general, but had poor specificity to correctly identify individuals at high risk. Most patients identified as false positives had substantial impairment in their mental health, involving, in some instances, psychotic-like experiences that did not reach the CAARMS threshold criteria for high risk; from the GPs' point of view the referrals were correct. These patients needed treatment and were referred to IAPT or secondary or tertiary mental health services. We considered the cost of diagnosing these referrals, but did not collect economic data associated with the treatment that they subsequently received elsewhere in the NHS. This information will be useful in future economic assessments in similar settings.

Another important finding is that the leaflet posted to GPs (low intensity) was no more effective in generating referrals of individuals with FEP or at high risk of developing psychosis than PAU (no intervention). This result has implications for future postal campaigns and referral guidelines to raise awareness of psychotic symptoms; although a relatively inexpensive strategy, our findings suggest that it has little or no worth.

Every practice randomly assigned to the high-intensity intervention was offered support and training in the form and frequency that best suited their particular needs, on the basis of the information gathered from the TPB sessions. During the 2 years of the intervention the liaison practitioners were rarely called upon by participating GPs for advice and support regarding potential referrals of individuals at high risk or to request additional training in between the two prearranged educational sessions. High GP workload and scarce time might have contributed to GPs not requesting additional assistance,[33,34] although GPs were willing to engage in discussions about previous referrals during the second educational session. Accordingly, liaison practitioners might have covered more practices, thus increasing cost-effectiveness.

Articles

Our study has several limitations. Our original intention was to randomise all practices in the study area without consent and so exceed the numbers of clusters needed in each arm indicated by our power calculations, but the research ethics committee decided that this approach was not acceptable.[10] Furthermore, our assumptions about the general epidemiology of psychosis have been updated since the protocol was developed. Areas of low income have a high prevalence of psychosis[35] and practices in our most deprived areas were most likely to decline being randomly assigned to an intervention, therefore we might have missed yield. This problem was not helped by initially including two ineligible practices. Thus, our statistical power was lower than intended, which could account for why the confidence limits for our primary effect included unity whereas those for FEP and the combined psychosis true-positive outcome were narrower—about the same doubling in the number of referrals.

The random assignment process was concealed and we took steps to mask allocation along with other design features to restrict the likelihood that bias led to our results. These approaches were robust within the limits of pragmatism, but probably not perfect. Verification of masking of the central administrator was shown by the fact that no referrals were rejected. Not all the surgeries had a comparable overall educational experience, GP staff changed during the trial, and the intention-to-treat approach was conservative. We militated against bias by offering practices several visits to ensure the maximum number of clinicians attended each session. However, some GPs inevitably arrived late or left early due to clinical commitments. Nevertheless, such GPs could still have been influenced by the cluster-level intervention, as ascertained by the authors of the TPB guidelines.[21] These nuances were not measured in our trial because the TPB questionnaires were anonymous to increase the chance of authentic responses. The time that the effect of the intervention persists and the optimum number of refresher sessions that are needed are not known. Future research should investigate these factors to achieve a balance between intervention effectiveness and cost-effectiveness, as additional educational booster sessions could be either unproductive or crucial to sustain identification of individuals at high risk or with FEP.

Contributors

JP was principal investigator, MP was project manager, and PBJ was the chief investigator for this trial. TJC and PBJ led the design of this trial. DAR elaborated the theoretical basis of the intervention. All authors contributed to the development of educational materials. JS and TJC did sample size calculations, statistical analysis, and random assignment of participants. HJ and SB did the economic evaluation. GS, EJ, and CC implemented the trial interventions. JPG provided valuable advice with regards to implementation and support needed in primary care. JP, DAR, SB, and PBJ drafted the manuscript. All authors provided a critical review and final approval of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We acknowledge funding support from a National Institute for Health Research (NIHR) Programme Grant for Applied Research programme (RP-PG-0606-1335; Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses) awarded to PBJ. The work forms part of the NIHR Collaboration for Leadership in Applied Health Research and Care East of England.

References

1 McCrone P, Craig TK, Power P, Garety PA. Cost-effectiveness of an early intervention service for people with psychosis. *Br J Psychiatry* 2010; **196:** 377–82.
2 Platz C, Albrecht DS, Cattapan-Ludewig K, et al. Help-seeking pathways in early psychosis. *Soc Psychiatry Psychiatr Epidemiol* 2006; **41:** 967–74.
3 Simon A, Lester HE, Tait L, et al. The International Study on General Practitioners and Early Psychosis (IGPS). *Schizophr Res* 2009; **108:** 182–90.
4 Phillips LJ, Leicester SB, O'Dwyer LE, et al. The PACE clinic: identification and management of young people at "ultra" high risk of psychosis. *J Psychiatr Pract* 2002; **8:** 255–69.
5 Hegelstad WT, Larsen TK, Auestad B, et al. Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. Am J Psychiatry 2012; **169:** 374–80.
6 Gilbody S, Whitty P, Grimshaw J, Thomas R. Educational and organisational interventions to improve the management of depression in primary care: a systematic review. *JAMA* 2003; **289:** 3145–51.
7 Power P, Iacoponi E, Reynolds N, et al. The Lambeth Early Onset Crisis Assessment Team Study: general practitioner education and access to an early detection team in first-episode psychosis. *Br J Psychiatry* 2007; **191** (suppl 51): 133–39.
8 Lester HE, Birchwood M, Freemantle N, Michail M, Tait L. REDIRECT: cluster randomised controlled trial of GP training in first-episode psychosis. *Br J Gen Pract* 2009; **59:** 183–90.
9 UK Department of Health. Policy paper. Mental health services: achieving better access by 2020. 2014. https://www.gov.uk/government/publications/mental-health-services-achieving-better-access-by-2020 (accessed Oct 28, 2014).
10 Perez J, Russo DA, Stochl J, et al. Comparison of high and low intensity contact between secondary and primary care to detect people at ultra-high risk for psychosis: study protocol for a theory-based, cluster randomized controlled trial. *Trials* 2013; **17:** 222.
11 Medical Research Council. Developing and evaluating complex interventions: new guidance. London: Medical Research Council, 2008.
12 UK Office for National Statistics. Households by deprivation dimensions: table QS119EW. Titchfield: Office for National Statistics, 2011.
13 Ryan P. RALLOC: stata module to design randomized controlled trials, 2010. http://EconPapers.repec.org/RePEc:boc:bocode:s319901 (accessed Feb 2, 2011).
14 Morrison AP, French P, Stewart SL, et al. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *BMJ* 2012; **344:** e2233.
15 Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust NZ J Psychiatry* 2005; **39:** 964–71.
16 Howe A, Ashton K, Hooper L. Effectiveness of educational interventions in primary care mental health: a qualitative systematic review. *Primary Care Commun* 2006; **11:** 167–77.
17 Foy R, Francis JJ, Johnston M, et al. The development of a theory-based intervention to promote appropriate disclosure of a diagnosis of dementia. *BMC Health Serv Res* 2007; **7:** 207.
18 Ajzen I. From intentions to action: a theory of planned behavior. In: Kuhl J, Beckman J, eds. Action control: from cognitions to behaviors. New York: Springer, 1985: 11–39.
19 Ajzen I. The theory of planned behavior. *Organ Behav Hum* 1991; **50:** 179–211.
20 Walker A, Watson M, Grimshaw J, Bond C. Applying the theory of planned behaviour to pharmacists' beliefs and intentions about the treatment of vaginal candidiasis with non-prescription medicines. *Fam Pract* 2004; **21:** 670–76.

© Perez *et al.* Open Access article distributed under the terms of CC BY.

21 Ajzen I. Constructing a TpB questionnaire: conceptual and methodological considerations, 2002 (revised 2006). http://www.uni-bielefeld.de/ikg/zick/ajzen%20construction%20a%20tpb%20questionnaire.pdf (accessed Feb 24, 2009).

22 Francis JJ, Eccles MP, Johnston M, et al. Constructing questionnaires based on the theory of planned behaviour. A manual for health services researchers. Newcastle upon Tyne: Centre for Health Services Research, University of Newcastle upon Tyne, 2004. http://openaccess.city.ac.uk/1735/ (accessed Feb 24, 2009).

23 Russo DA, Stochl J, Croudace TJ, et al. Use of the theory of planned behaviour to assess factors influencing the identification of individuals at ultra-high risk for psychosis in primary care. *Early Interv Psychiatry* 2012; **6:** 265–75.

24 Kirkbride JB, Fearon P, Morgan C, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3–centre AeSOP study. *Arch Gen Psychiatry* 2006; **63:** 250–58.

25 Vuong QH. Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica* 1989; **57:** 307–33.

26 McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. *Psychol Methods* 1996; **1:** 30–46.

27 The R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2014.

28 Simon A, Jegerlehner S, Müller T, et al. Early schizophrenia in primary care: a randomized sensitization study. *Br J Gen Pract* 2010; **60:** 353–59.

29 Reynolds N, Wuyts P, Badger S, Fusar-Poli P, McGuire P, Valmaggia L. The impact of delivering GP training on the clinical high risk and first-episode psychosis on referrals and pathways to care. *Early Interv Psychiatry* 2014; published online March 6. DOI:101111/eip.12126.

30 Michie S, Johnston M, Francis J, Hardemann W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. *Appl Psychol Int Rev* 2008; **57:** 660–80.

31 Linscott RJ, van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychol Med* 2013; **43:** 1133–49.

32 Stochl J, Khandaker GM, Lewis G, et al. Mood, anxiety and psychotic phenomena measure a common psychopathological factor. *Psychol Med* 2014; **14:** 1–11.

33 Hummers-Pradier E, Scheidt-Nave C, Martin H, Heinemann S, Kochen MM, Himmel W. Simply no time? Barriers to GPs' participation in primary health care research. *Fam Pract* 2008; **25:** 105–12.

34 Jowett SM, Macleod J, Wilson Hobbs FD. Research in primary care: extent of involvement and perceived determinants among practitioners from one English region. *Br J Gen Pract* 2000; **50:** 387–89.

35 Kirkbride JB, Jackson D, Perez J, et al. A population-level prediction tool for the incidence of first-episode psychosis: translational epidemiology based on cross-sectional data. *BMJ Open* 2013; **3:** e001998.

Appendix 8 Use of the theory of planned behaviour to assess factors influencing the identification of students at clinical high-risk for psychosis in 16+ education

Russo *et al. BMC Health Services Research* (2015) 15:411
DOI 10.1186/s12913-015-1074-y

BMC Health Services Research

RESEARCH ARTICLE Open Access

Use of the Theory of Planned Behaviour to assess factors influencing the identification of students at clinical high-risk for psychosis in 16+ Education

Debra A. Russo[1,2*], Jan Stochl[1,2], Michelle Painter[1], Gillian F. Shelley[1], Peter B. Jones[1,2,3] and Jesus Perez[1,2]

Abstract

Background: The longer psychotic disorders are untreated the worse their prognosis. Increasing the awareness of early psychosis by professionals who come into regular contact with young people is one strategy that could reduce treatment delay. As teachers engage with students on a daily basis, their role could be exploited to increase awareness of the early signs of psychosis. This study employed the Theory of Planned Behaviour (TPB) to identify and measure factors that influence identification of students at high-risk (HR) of developing psychosis in 16+ educational institutions.

Methods: An elicitation phase revealed beliefs underlying teachers' motivations to detect HR students and informed the construction of a preliminary 114-item questionnaire incorporating all constructs outlined in the TPB. To define the determinants of teachers' *intention* to identify HR students, 75 teachers from secondary and further education institutions in 12 counties surrounding Cambridgeshire completed the questionnaire. A psychometric model of item response theory was used to identify redundant items and produce a reduced questionnaire that would be acceptable to teachers.

Results: The final instrument comprised 73 items and showed acceptable reliability ($\alpha = 0.69$-0.81) for all direct measures. Teacher's confidence and control over identification of HR students was low. Although identification of HR students was considered worthwhile, teachers believed that their peers, students and particularly their managers might not approve. Path analysis revealed that direct measures of *attitude* and *PBC* significantly predicted *intention,* but *subjective norm* did not. *PBC* was the strongest predictor of *intention*. Collectively, the direct measures explained 37 % of the variance of *intention* to identify HR for psychosis.

Conclusions: This research demonstrated how the TPB can be used to identify and measure factors that influence identification of students at HR of developing psychosis in 16+ educational institutions and confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire for teachers. Consideration of the key determinants of identification in schools will facilitate the design of successful educational intervention strategies with the potential to reduce treatment delays for HR students.

Keywords: Early intervention, Psychosis, High risk, TPB questionnaire, Schools, Teachers, Intention

* Correspondence: dr335@medschl.cam.ac.uk
[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Block 7, Ida Darwin Site, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EE, UK
[2]Department of Psychiatry, University of Cambridge, Cambridge, UK
Full list of author information is available at the end of the article

BioMed Central

© 2015 Russo et al. **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

© 2015 Russo *et al.* Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Background

The longer psychotic disorders are untreated the worse their prognosis [1–3], with some individuals remaining untreated for up to 2 years [4]. This finding has led to efforts to detect psychotic disorders early to minimise the developmental [5], social [6] and biological [7] deterioration that can occur after a prolonged duration of untreated psychosis (DUP). Increasing the awareness of signs and symptoms of early psychosis by professionals who come into regular contact with young people is one strategy that has been investigated to reduce treatment delay. Indeed, this approach has been recommended by the UK Department of Health [8]. Thus, if we could identify people who might be at clinical high-risk for psychosis (HR), we could also increase opportunities to reduce DUP. The importance of this is corroborated by the finding that the risk of developing psychosis is several hundred times higher in individuals that meet the high risk criteria when compared to the general population [9].

Initial psychotic symptoms typically have their onset and maximum impact in late adolescence and early adulthood [10]. It has been reported that adolescents (up to the age of 18) have a longer DUP than adults (over 18) [11]. Although it has been claimed that general practitioners (GPs) are most frequently the first contact when a young person is developing psychosis [12], it is of concern that other findings indicate adolescents rarely seek help from GPs concerning their emotional well-being and those with mental health problems do not visit the GP more frequently than those without them [13]. In light of the fact that teachers come into contact with students on a daily basis, sometimes for several hours at a time, their role could be exploited to increase awareness of the early signs of psychosis and speed up the referral of these potentially at risk students to Early Intervention Services (EIS).

Two intensive health promotion and information campaigns have included components that provided knowledge about early symptoms of psychosis to teachers [14, 15]. Both studies claimed to increase referrals to early detection teams and to significantly reduce DUP. However, the number of referrals specifically from the teachers was not reported. Mental health literacy training programmes for teachers have resulted in increased knowledge of the early signs of psychosis [16] and earlier, more appropriate referrals of pupils to mental health services [17, 18]. Indeed, a recent systematic review recommended the development of initiatives targeting non-health service professionals, such as teachers, to enhance help-seeking behaviour and therefore reduce service delays [19].

To date, only two studies have evaluated teacher's knowledge concerning psychotic symptoms and how to access help for these individuals [20, 21]. Although teachers may be in a fundamental position to identify possible signs of psychosis and the majority are able to recognise these symptoms in their students, they are less likely to be aware of the mental health services available for young people or know how to access the appropriate help and services [20, 21]. The additional finding that teachers are willing to engage in further training in this area and co-operate with specialist teams to obtain support [20, 21] suggests an educational intervention to raise awareness and increase referrals of students at HR for psychosis in this group of professionals will be fruitful. However, unlike the more discernable symptoms of psychosis, identifying young people who might be in the prodromal phase of a psychotic illness is more challenging. The earliest signs of a psychotic disorder are multifaceted, non-specific and have common characteristics with the initial stages of other disorders [10]. This indicates the need for in-depth training to help teachers correctly identify the symptoms and those most at risk.

Before attempting to design an educational programme to help teachers detect students who may be at HR of developing psychosis, it is necessary to explore the factors that are currently influencing their identification. To our knowledge, no research to date has attempted to identify factors that influence the detection of students at risk of developing psychosis in schools. If it is assumed that teacher's identification of HR students is a form of human behaviour, it can be described in terms of general theories relating to human behaviour. This provides a theoretical framework to help identify key determinants of that behaviour and propose options for its modification.

Interventions to change professional practice are often limited by the lack of an explicit theoretical and empirical basis [22]. The use of theory advances behavioural science [23] because it provides a generalisable framework for predicting and interpreting behaviour, informs the design of interventions and enables the evaluation of potential causal mechanisms [24].

Theoretical framework

The Theory of Planned Behaviour [TPB; 25, 26] (Fig. 1) was selected because it provides clear definitions of constructs and is supported by a comprehensive body of correlational evidence [27]. The TPB provides a simple and efficient framework for use in the investigation of an individual's intent to perform context-specific actions. The TPB assumes that the majority of human behaviour is goal-directed, socially influenced [25], and that individuals are logical and rational in their decision making [28]. It is a deliberative processing model that implies individuals make behavioural decisions based on careful consideration of available information [29]. In addition, it recognises the necessity of estimating the extent to which the individual is capable of exercising control over the behaviour in question [30]. The model's ability to consider internal (e.g. abilities; knowledge) and external

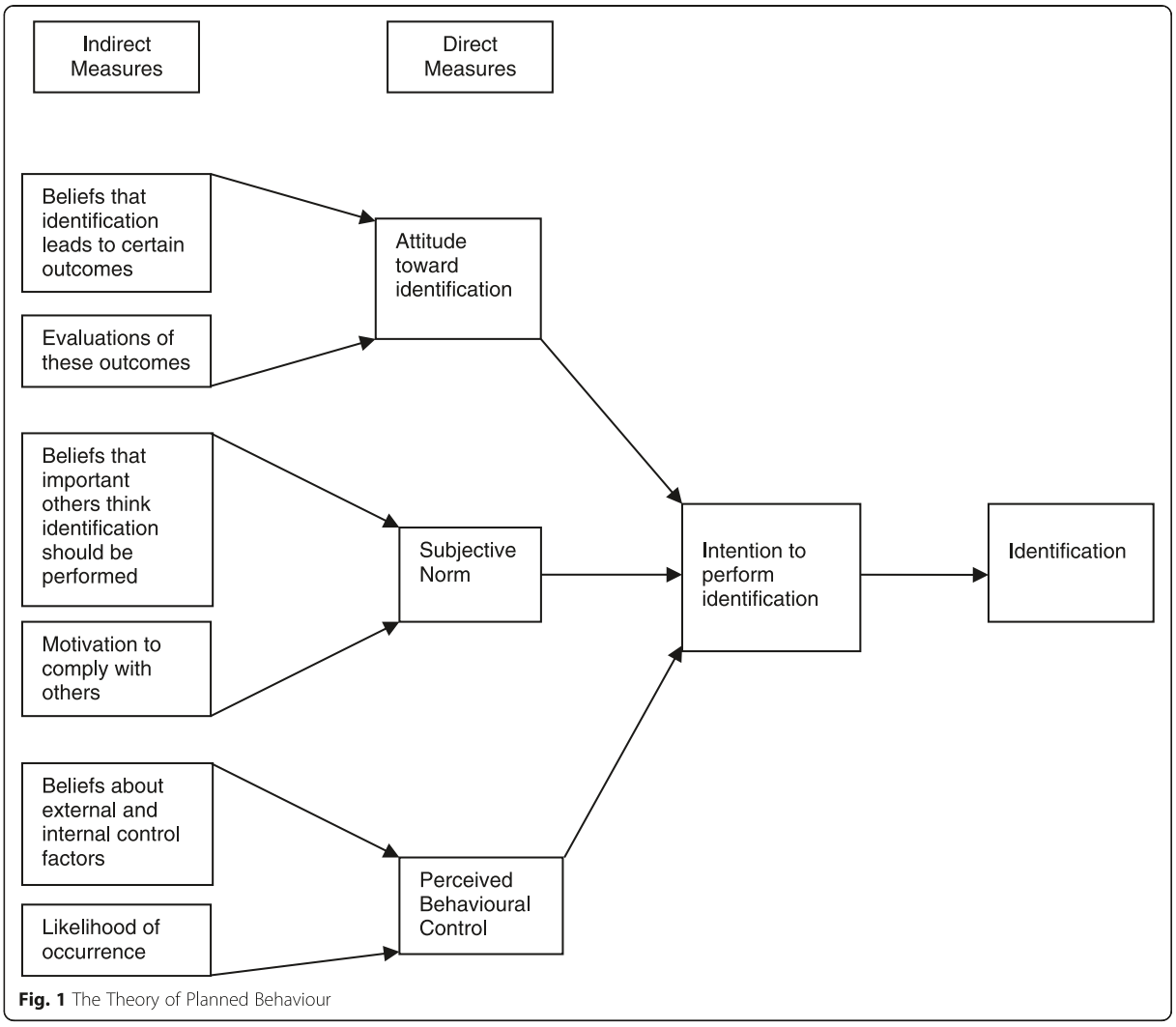


Fig. 1 The Theory of Planned Behaviour

(e.g. opportunity; cooperation of others) control factors in relation to performing a behavior [31] is important in professional contexts such as educational institutions, where both factors may influence teacher's behaviour.

The TPB proposes that the act of identifying students at HR for psychosis during the school day is predicted by the strength of a teacher's *intention* to identify these students. This *intention* is guided by three considerations: the teacher's personal evaluation of engaging in the identification of HR students (*attitude*); the intensity of social pressure from salient referents that the teacher perceives regarding the adoption of this behaviour (*subjective norm*) and the perceived ease or difficulty of identifying HR students based on both past experience and anticipated barriers (*perceived behavioural control*; *PBC*) [26].

The TPB has also been used to explain teachers' intentions and behavior in the classroom [e.g.32, 33]. However, only one study has used the TPB to predict teachers' intentions to refer students to mental health professionals [34]. Intentions were predicted by all the TPB variables; which accounted for 58 % of the variance associated with predicting their intention to refer.

This study describes the design and testing of items for a self-completion questionnaire to be used within 16+ educational institutions to identify and measure the factors that influence the identification of students at HR for psychosis using TPB. Results from this phase would inform the subsequent design of educational programs to evaluate the most effective way to help teachers identify these students.

Method

We followed the guidelines outlined by the co-author of the TPB [35] and reviews of current standard practice for its application [29]. We were also guided by

© 2015 Russo *et al.* Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

recommendations from other researchers in this field [36]. The behaviour under investigation was defined as "*identifying students at HR for psychosis during the school day*".

Phase 1: Questionnaire development

Observing the theory, the three predictors of intention were measured by two methods. Firstly, 'directly', by asking teachers to summarise their overall i) evaluative reaction to the identification of students at HR for psychosis (*attitudes*), ii) perceptions of whether important others would approve of or be likely to engage in the identification of students at HR (*subjective norms*) and iii) perception of having, or not having control over the identification of students at HR for psychosis (*PBC*). Secondly, 'indirectly', by asking teachers about their specific beliefs associated with forming *attitudes*, *subjective norms* and *PBC* related to the identification of students at HR. These indirect measures are presumed to determine the more global reactions of the direct measures [26].

Development of 'indirect' measures

The objective of this phase was to elicit commonly held beliefs about identifying HR students from teachers. This enabled the development of questionnaire items based on these salient beliefs. Beliefs are central to the TPB; they provide the cognitive and affective foundations for *attitudes, subjective norms*, and *PBC* [35]. An accurate understanding of the specific beliefs associated with identifying students at HR for psychosis provides insight into why teachers may execute particular behaviours [35]. Therefore, this information can be important in the design of effective educational interventions.

Procedure

Two teachers working outside of the study boundaries were recruited to complete an elicitation questionnaire to help identify salient beliefs underlying motivations to identify students at HR for psychosis during the school day. Each was emailed a series of 12 questions to determine:

1. Behavioural Beliefs: most frequently perceived advantages and disadvantages associated with identification
2. Normative Beliefs: most important people or groups who would disapprove or approve of identification
3. Control Beliefs: perceived barriers or facilitating factors associated with identification

To represent a variety of experiences within the final questionnaire the respondents were instructed to discuss these issues with colleagues so that the answers reflected both personal experience and also that of other teachers.

Analysis

Two researchers independently analysed the content of the responses to identify the beliefs for each of the three predictor variables. These are are summarised below:

Behavioural beliefs

Positive

1. Facilitates help with their particular problems
2. Avoids friends and peers withdrawing due to negative interpretation of symptoms
3. Avoids staff misinterpreting student's symptoms as lack of interest
4. Increases awareness and understanding
5. Avoids disruption to other students in class
6. Being able to help and counsel appropriately
7. Having a positive attitude to mental health
8. There are positive outcomes for those identified at risk

Negative

1. Students at HR should not be at school/college
2. I am wary of students with mental health problems
3. Labelling associated with identification
4. Identified students will be treated differently - stigma
5. Students wrongly diagnosed by a teacher
6. Lack of knowledge in how to cope with young people with psychosis
7. Negative preconceived ideas about how a student will react to identification
8. Belief that it is not their responsibility to identify someone at risk

Normative beliefs

1. Impact from student's family has to be considered
2. Parents/carers may disapprove
3. Students may disapprove
4. Educational system does not encourage identification students at risk (e.g. LEA/school/college/staff union/departmental policies, government guidance)
5. Senior management teams at school/college are unwilling to accept that students at risk are an issue

Control beliefs

Barriers

1. Difficulties in coping when dealing with students with psychosis.
2. Lack of understanding about early psychosis.
3. Fear of getting it wrong.
4. Fear of repercussions from student/family
5. Expressing concern is only effective if there is a school-wide procedure for investigating those concerns.

6. Not knowing where to go for advice and help if they suspect a student is suffering
7. Time restrictions
8. Feeling pressurised in their job
9. Not being able to recognise the at risk symptoms

Facilitators

1. Access to information, knowledge and resources
2. Having a designated member of staff to coordinate the care of students who may demonstrate signs of being at risk

Following this stage, a questionnaire item was constructed to assess the strength of each behavioural, normative and control belief. Additionally, a corresponding item was developed to assess the impact each belief might have on identifying HR student (Table 1). These indirect items and their format were then agreed by the entire research team, to ensure that each belief was represented in the questionnaire.

Development of 'direct' measures

Direct measures are a summary estimate of a teacher's global *attitude, subjective norm* and *PBC* towards identifying students at HR for psychosis; and predictors of *intention* to perform such identification [36]. *Intention* captures the motivational factors that influence behaviours [31] and signifies a teacher's decision to exert effort to attempt identification [26].

Procedure

According to the TPB guidelines, the direct measures were tailored to specific behaviours and samples [36]. This process should not be guided by an arbitrary selection of questions or adopted items from previous studies [35]. Therefore, appropriate items for the target population (teachers of 16+ students) and specific context (during the teaching day) were agreed by the research team to reflect each direct construct (Table 2).

Phase 2: Questionnaire construction

A 114-item preliminary version of the questionnaire was constructed including indirect and direct measures for a*ttitude, subjective norm, PBC and intention*. The questionnaire included instructions regarding its completion and an introduction about how an individual at HR for psychosis might present in consultation. Feedback questions concerning ambiguity, content, missing factors and format guided any necessary subsequent refinements. Finally, socio-demographic questions were added to describe the sample.

Phase 3: Questionnaire evaluation and refinement

The aim of this phase was to evaluate the acceptability and feasibility of administering the questionnaire within a representative sample of teaching staff in 16+ educational institutions, in addition to evaluating its reliability.

Procedure

Questionnaires and information sheets were posted to 790 teachers working at secondary schools with a sixth form (N = 13), sixth form colleges (N = 2) and further education colleges (N = 4) across 12 counties in the UK between November 2009 and May 2010. These educational institutions were selected via a Google® search for 'Secondary and Further Education institutions in the counties surrounding Cambridgeshire'. Selection criteria included 1) institutions with high quality prospectuses 2) websites that provided contact names for the various courses on offer. The information sheet outlined all ethical issues and contained sufficient information to allow teachers to decide whether they consented to take part in the study or not. A postal reminder was sent to non-respondents three weeks later.

Ethical approval was granted by the Cambridgeshire East Research Ethics Committee as part of the NIHR research programme RP-PG-0606-1335.

Table 1 Examples of questionnaire items assessing indirect Attitude, Subjective Norm and PBC

Belief Strength	*N* Items	Sample Item	Impact of Belief	*N* items	Sample Item
Attitude	11	If I were to identify students at risk of developing psychosis at school or college it would maintain their social functioning (e.g. support networks & relationships)	Outcome evaluation for each attitudinal belief	11	Maintaining social functioning of students is unimportant-important : *Extremely unimportant - extremely important*
Subjective Norm	5	The student's family think I should identify a student at risk of developing psychosis at school or college	Motivation to comply with each group or individual	5	How much do you care what a student's family think you should do? *Not at all – very much*
Perceived Behavioural Control	10	We have a school/college-wide procedure for identifying students at risk of developing psychosis	The power each control belief exerts	10	Having a school/college-wide procedure would make identifying students at risk of developing psychosis : *Less likely – more likely*

© 2015 Russo *et al.* Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Table 2 Examples of questionnaire items measuring direct Attitude, Subjective Norm, PBC and Intention

TPB Construct		*N* Items	Sample Item
Attitude		8	Identifying a student at risk of developing psychosis at school/college would be *Harmful/beneficial*
Subjective Norms		4	People whose views I value within my profession would disapprove of me identifying students at risk of developing psychosis: *Strongly agree – strongly disagree*
Perceived Behavioural Control	Self-Efficacy	3	Identifying students at risk of developing psychosis at school/college would be: *Difficult- easy*
Controllability		2	The decision to identify students at risk of developing psychosis at school/college is beyond my control: *Strongly agree – strongly disagree*
Intention	Intention	3	I am committed to identifying students at risk of developing psychosis at school/college: *Strongly agree – strongly disagree*
Self-prediction		1	I expect to identify students at risk of developing psychosis at school/college :*Strongly agree – strongly disagree*

Analysis

A psychometric evaluation of the questionnaire was conducted to confirm that information obtained using a reduced-item final tool would still provide a sound basis for decision making.

A modern approach, in the form of a psychometric item response model – the polytomous graded response model [37] was used to examine the validity of each item within direct and indirect measures and to inform decisions regarding the removal of items. The internal consistency of the direct measures of *attitude, subjective norm and PBC* was assessed using Cronbach's Alpha coefficient on both the original and reduced-item questionnaires. An internal consistency criterion is inappropriate for the evaluation of reliability of indirect measures [35], because they are formative rather than reflective indicators of the underlying construct [38]. Alternatively, correlations between direct and indirect measures of the same construct were calculated to confirm the convergent validity of the indirect measures. Confirmatory factor analysis [39] was conducted on all measures to assess the relative importance of each item on the total construct; thus confirming the structural conformity of the final questionnaire with the TPB. The relationship between *intention* and the indirect and direct measures were investigated using path analysis, with "*intention*" specified as the dependent variable. Path analysis was used to reveal the degree of fit between the TPB and actual data, in addition to providing an estimation of multiple regression equations linking the TPB variables [40].

Data were analysed using the statistical software package NCSS Version 7.1 [41] for descriptive statistics; item analysis for the purpose of identifying redundant items for removal from the questionnaire was conducted using MULTILOG and confirmatory factor analysis and path analysis was performed with Mplus Version 6.1 [42].

Results

Descriptive statistics of the respondents

Seventy five (9.5 %) teachers returned questionnaires. The mean time taken to complete the questionnaire was reported as 20.1 (SD = 9.6) minutes. The mean age of participating teachers was 44.3 (SD = 10.9). More female teachers (N = 50; 67 %) than male teachers (N = 25; 33 %) completed and returned the questionnaire. The mean number of years teachers had been teaching was 13.7 (SD = 10.6). The majority of the sample (N = 62; 83 %) reported never attending any kind of mental health training during their careers. Teachers reported average class sizes of 17 (SD = 6.3) students and estimated that the mean number of students they taught with a mental health problem was 5 (SD = 7.6).

Psychometric properties of the questionnaire

Validity

The polytomous graded response model [37] was used to study the validity of items within specific constructs. Also, distribution of responses for each item was assessed. This allowed the identification of items that required rewording, and those that were redundant because they added little information or offered similar response patterns. For the indirect measures, items were eliminated because of their ambiguity or similarity to other items. Final decisions on item exclusion were based on extensive discussions within the research team to avoid invalidation of the questionnaire due to exclusion of essential items that had emerged during the elicitation procedure. Forty-three items were excluded, resulting in a 73-item final questionnaire. Subsequent analyses were conducted on this reduced scale.

Pearson's correlations between the indirect and direct measures of the corresponding construct indicate whether indirect measures are well constructed and adequately cover the breadth of the measured construct [43]. With the exception of *PBC,* each set of indirect beliefs was highly correlated with their direct predictor of *intentions*: behavioural beliefs with *attitudes* ($r = 0.43$; $p < 0.001$); normative beliefs with *subjective norms* ($r = 0.61$; $p < 0.001$); and control beliefs with *PBC* ($r = 0.28$; $p < 0.023$).

Factor analysis was used to assess the structural conformity of the final questionnaire with the TPB. The

resulting standardized coefficients can be interpreted as correlations between the measured construct and corresponding item. Higher coefficients indicate higher factor validity. Therefore, these items are superior at discriminating between teachers with low and high levels of the corresponding latent construct.

Table 3 shows the items with the highest factor validity within direct and indirect measures. Only one item within (each) direct *subjective norms,* direct *PBC*, indirect *attitude* and two items within indirect *subjective norms* showed a factor validity lower than 0.5. However, indirect *PBC* was less coherent. All items within this construct showed low intercorrelations, in accordance with Azjen's [35] premise that internal consistency is not a necessary feature of indirect measures. Therefore, the use of factor analysis is questionable for this construct. The factor validity is reported mainly for completeness and should be interpreted with caution.

Reliability

The lower bound estimates of reliability assessed by Cronbach's alpha for the original and reduced questionnaires are shown in Table 4. An acceptable level of α was set at >0.60 [35]. The values confirmed improvement for *subjective norms* and *PBC* in the reduced version. However, measurement precision for *intention* and *attitude* was slightly reduced but still large enough to be interpreted as acceptable. As a greater number of items in the questionnaire can artificially inflate the value of alpha [44] it was decided that a shorter questionnaire would be more acceptable to teachers and therefore a slightly reduced alpha was an acceptable compromise.

Distribution of teachers' scores for all TPB constructs

For the direct measures, including *intention*, the mean of the item scores was calculated to provide an overall construct score (See Table 3 for item scoring ranges). Beliefs are structured according to an expectancy-value framework. Individuals hold expectancies about the outcomes they anticipate if they behave in a particular way. Simultaneously, they also hold beliefs about the value of that outcome [26]. Therefore, indirect measures are calculated by multiplying individual belief components and then summing the products. For example, indirect *attitude* is calculated by multiplying the perceived likelihood of a particular outcome of the behaviour (behavioural belief strength) by the evaluation of that outcome (outcome evaluation) The resulting products are summed across all beliefs to create an overall attitude score (See Table 3 for the corresponding *subjective norm* and *PBC* belief components)

Table 5 summarises data obtained from the questionnaires. Higher scores indicate that a teacher intends to, is in favour of, experiences social pressure to, and feels in control of identifying students who may be at HR for psychosis.

For indirect measures, mean scores reflected overall weakly positive attitudes towards identification, almost no favourable pressure to perform identification and very low control over the identification of students at HR for psychosis. *Subjective norm* was the lowest (3.1), which

Table 3 Items with the highest factor validity within indirect and direct measures

Direct Measures		**Item**	**Scoring**	**Factor Validity**
Attitude		If I were to identify students at risk of developing psychosis at school or college, it would be *Inappropriate/appropriate* (for my role)	+1 - +7	r = 0.76
Subjective Norm		It is not expected of me that I identify at risk of developing psychosis at school or college *Strongly Agree/Disagree*	+1 - +7	r = 0.90
Perceived Behavioural Control		I am confident that I could identify students at risk of developing psychosis at school or college if I wanted to *Strongly Agree/Disagree*	+1 - +7	r = 0.89
Indirect Measures		**Item**	**Scoring**	**Factor Validity**
Attitude Belief components:	Behavioural beliefs *X*	If I were to identify students at risk of developing psychosis at school or college it would increase awareness and understanding of mental health issues *Strongly Agree/Disagree*	+1 - +7	r = 0.90
	Outcome evaluation	Increasing awareness and understanding of mental health issues at school or college is Unimportant/Important	−3 - +3	
Subjective Norm Belief components:	Normative beliefs *X*	The senior management team within my school thinks I should identify students at risk of developing psychosis at school or college *Strongly Agree/Disagree*	−3 - +3	r = 0.97
	Motivation to comply	How much do you care what the senior management team within your school thinks you should do? *Not at all/Very much*	+1 - +7	
Perceived Behavioural Control Belief components:	Control beliefs *X*	I have knowledge of a student's mental health history at school or college *Rarely/Frequently*	+1 - +7	r = 0.76
	Influence of control	Knowledge of my student's mental health history would make identifying a identify student at risk of developing psychosis at school or college *Difficult/Easier*	−3 - +3	

© 2015 Russo *et al.* Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Table 4 Cronbach's alphas for the direct measures of the original and reduced form questionnaires

Direct Measures	Original Questionnaire 114 items	Reduced Questionnaire 73 items
Intention	0.82 (2.56)	0.81 (2.63)
Attitude	0.82 (3.67)	0.74 (3.86)
Subjective Norms	0.62 (3.45)	0.69 (2.77)
PBC	0.66 (3.54)	0.75 (2.91)

indicates a very weak level of positive control. *Attitude* was the highest, but still a low score (123.9).

Mean scores for direct measures were just above the mid-scale score for *intention* and *attitude*, and just below the mid-scale score for *subjective norm* and *PBC*. This suggests that teachers considered identifying students at HR for psychosis a worthwhile behaviour and would attempt identification during the school day. However, they believed that their peers or superiors might not approve this. Moreover, their confidence and control over identification was low.

Prediction of 'intention'

Path analysis revealed that only direct measures of *attitude* and *PBC* significantly predicted *intention. Subjective norm* did not predict *intention. PBC* was the strongest predictor of *intention* (regression coeff. = 0.46, $p < 0.01$), followed by *attitude* (0.39, $p < 0.01$).

Collectively, the direct measures explained 37 % of the variance of *intention* to identify HR for psychosis.

Discussion

The purpose of this research was to design a questionnaire to expose and measure factors that might contribute to a teacher's decision to attempt identification of students that may be at clinical HR of developing psychosis. This study was conducted because there was no evidence in the literature of the influence of the motivations and barriers teachers experience when making this decision.

Results from the analysis of the indirect measures revealed that increasing awareness and understanding of mental health issues was a source of personal positive beliefs, as demonstrated by the item with the highest factor validity within the indirect *attitude* construct. Notably, all normative beliefs were negative. The perception was that students, student's family, professional colleagues and the educational system would not encourage the identification of students at HR for psychosis. The item with the highest factor validity indicated that a key source of social pressure came from the senior management team within school. The proposal that control beliefs should comprise separate measurement of controllability and self-efficacy [45] was supported by our study. However, control factors were the primary influence for control beliefs. The item with the highest factor validity indicated that knowledge of the student's personal and family mental health history was an important facilitator of *PBC*. Facilitators of self-efficacy included access to support and the provision of a designated member of staff to co-ordinate the care of students. Lack of understanding and knowledge were the main barriers to self-efficacy. These findings replicated previous work revealing factors that might prevent teachers' identifying psychotic symptoms in students [20, 21], thus demonstrating the validity of our questionnaire.

These results suggest a reoccurring theme of beliefs underlying a teacher's decision to attempt identification of a student that might be at HR of developing psychosis: lack of access to information, knowlege and resources will all hinder teacher's ientification behaviour. Identifying these particular beliefs reveals why teachers hold certain attitudes, subjective norms, and perceptions of behavioral control in relation to identifying students at risk of developing psychosis. This demostrates the value of using the TPB for designing effective programs to change teacher's behavior. Equipped with this information, effective strategies can be designed to target these facilitators and barriers towards identification of at risk students.

Results from the analysis of the direct measures revealed that most teachers had positive *intentions* and

Table 5 Descriptive statistics of Teachers' responses for the indirect and direct measures

Indirect Measures	**Final no. of items**	**Mean**	**Standard Deviation**	**Standard Error**	**Minimum Score**	**Maximum Score**	**Possible range of total scores**
Attitude	22	123.9	51.1	6.11	–5	225	- 231 to + 231
Subjective Norm	10	3.1	28.0	3.26	–65	65	- 105 to + 105
PBC	20	29.7	27.1	3.13	–64	95	- 210 to + 210
Direct Measures	**Final no. of items**	**Mean**	**Standard Deviation**	**Standard Error**	**Minimum Score**	**Maximum Score**	**Mid-Scale Score**
Intention	4	16.5	6.0	0.70	4	28	16
Attitude	8	39.9	7.6	0.88	8	56	32
Subjective Norm	4	14.7	5.0	0.58	4	28	16
PBC	5	18.5	5.8	0.67	5	35	20

attitudes towards identifying students at HR for psychosis. However, mean scores for each direct construct were around the mid-scale score, indicating scope for modification and improvement. The mean *PBC* score indicated a degree of negativity about control, suggesting that identifying students at HR was somewhat difficult for teachers, both in terms of self-efficacy and perceived control concerns. *Intentions* to identify HR students were most strongly predicted by *PBC*. This implies teachers' perceptions of how confident they are that they are capable of identification and how much control they have over identification, are prominent motivational factors. This influence of *PBC* was also found in Lee's work [34] with teachers and is consistent with previous research that reports teachers with lower self-efficacy referred fewer students to a student support team [46]. Accordingly, effective interventions would need to prioritise the development of strategies that targeted this potential causal mechanism to prompt behavioural changes in this population.

Our questionnaire proved to be reliable, with the analysis supporting the predictive power of the TPB with regards to *intention*. The combination of *attitude, subjective norm* and *PBC* explained 37 % of the variance of *intention* to identify students at HR for psychosis. This is almost equivalent to the average percentage (39 %) of explained variance in *intention* reported for a variety of behaviors in the latest meta-analytic review of the TPB [31]. Interestingly, *subjective norm* was the only direct measure not to perdict intention, supporting previous studies that proposed that *subjective norm* was the weakest explanatory variable of intention [31].

It appears the control factors identified in the elicitation exercise did not capture adequately all the important considerations related to *PBC*. We suspect that the low correlation between direct and indirect *PBC* was due to the lack of reliability for indirect *PBC*. There are several possible explanations for this result. Firstly, items within indirect measures are not expected to correlate strongly with each other as they reflect a dynamic latent construct [35]. Secondly, teachers' *PBC* beliefs toward identifying students at HR of developing psychosis could be ambivalent if they believe that it is likely to produce positive as well as negative outcomes [35]. Thirdly, the *PBC* construct generated beliefs with the greatest diversity, therefore, fewer items were removed during validity analysis, with the aim of retaining important beliefs that influence teachers' perceptions of control. However, to create a questionnaire of acceptable length, valid items might have been excluded. Finally, the way in which teachers conceptualise the notion of control and difficulty [47] could have contributed to the discrepancy. For example, teachers may believe that identification of students at HR for psychosis is under their control, whilst also considering identification difficult to carry out. Consequently, the inclusion of numerous different aspects of control within the constructs could be a major contributory factor to the low correlation.

These propositions imply that the identification of HR students is intrinsically challenging for teachers, especially when considering identification is not straightforward for clinicians and researchers in the field with specialist training. However, if interventions to educate teachers focus on the providing skills and strategies for the identification of symptoms rather than an actual 'diagnosis' of HR, referral of HR students could be achieved. Additionally, the use of a dedicated liaison practitioner to provide ongoing support and augment training with this potentially challenging task would be advantageous.

The major strengths of this study were the thorough psychometric evaluation of our TPB questionnaire and the explicit theoretical framework. Since the majority of TPB questionnaires are used only once with a specific population and behaviour, a thorough psychometric evaluation is usually considered non-feasible and therefore omitted [48]. Our research provides an empirically-supported theoretical basis for the design of interventions in 16+ educational institutions to improve the identification of students at HR for psychosis.

Despite strenuous efforts, the response rate to our questionnaire was poor. The low response rate (9.5 %) from the invited sample (N = 790) was the most important limitation of the study, and potential risk of bias for the findings. External validity could have been undermined if respondents differed systematically from non-respondents, e.g. more positive attitude towards identification. However, the respondents were from a variety of locations with varying years of teaching experience, in a diverse selection of subjects and positions which arguably provides a representative sample of the target population and increases the generalisability of the results. It was not possible to conduct a detailed analysis of non-responses as the necessary sociodemographic information was not accessible. Nevertheless, future work should aim to increase the response rate.

It is not possible to fully understand why teachers chose not to respond to the questionnaire. However, research has revealed strategies that may help future studies to increase their sample. The majority of strategies outlined in a recent review [49] of methods to influence responses to postal questionnaires were applied in the present study. However, sending questions by recorded delivery, providing non-respondents with a second copy of the questionnaire and contacting participants before sending questionnaires all increased response rates and should also be considered by future research. Furthermore, the most effective strategy, if funds allow, is a monetary incentive, as response rates can be more than doubled when payment is offered [49]. Nevertheless, questionnaire length would remain the limiting factor as the TPB requires the inclusion of many items

© 2015 Russo *et al.* Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

if it is to be used effectively to provide important insights into the issues that could be targeted to motivate behaviour change. The questionnaire in the present study was five pages long and it has been suggested that the optimum length is four pages [49]; hence efforts should be made to achieve this without compromising the theoretical content.

Our findings may have been limited by the use of self-reports as measures of beliefs and intention. As a result, the respondents might have unintentionally ('social desirability') or intentionally ('faking good') [50] expressed themselves more positively toward the identifying at risk students than they really were. However, inclusion of further questions in the questionnaire to assess this was not feasible. The questionnaires were already long enough to discourage some teachers from responding. Also, previous studies suggested that social desirability had a minimal impact on TPB models [51]. Moreover, returned questionnaires were anonymous, with no incrimination or benefits from participating. Also, current behaviours were not measured. Future research should not only rely on self-reports but include objective measures of behaviour.

Conclusions

This research demonstrated how the Theory of Planned Behaviour can be used to identify and measure factors that influence identification of students at HR of developing psychosis in 16+ educational institutions. We have confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire to identify teachers' beliefs and intentions concerning the identification of students at clinical HR for psychosis. Detection of the key determinants of identification will suggest avenues for modification and facilitate the design of successful educational intervention strategies.

The questionnaire is available from the authors.

Abbreviations

DUP: Duration of untreated psychosis; EIS: Early intervention services; GP: General practitioner; HR: Clinical high-risk for psychosis; PBC: Perceived behavioural control; TPB: Theory of planned behaviour.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PBJ is the chief investigator for this study. JP and MP are principal investigator and project manager, respectively. All authors participated in the design of the study. DAR elaborated the theoretical basis of the project and was responsible for the data collection. GS participated in the implementation of the study. Statistical analyses were carried out by JS. JP and DAR drafted the manuscript. All authors provided a critical review and final approval of the manuscript.

Authors' information

Not applicable.

Availability of data and materials

Not applicable.

Acknowledgements

The authors acknowledge funding support from NIHR programme grant RP-PG-0606-1335 'Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses'. They thank the LEGS study team (Erica Jackson, Chris McAlinden and Carolyn Crane) and all members of CAMEO services for their help and support in the elaboration of this trial.

Author details

[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Block 7, Ida Darwin Site, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EE, UK. [2]Department of Psychiatry, University of Cambridge, Cambridge, UK. [3]NIHR Collaboration for Leadership in Applied Health Research & Care, Cambridge, UK.

Received: 30 June 2014 Accepted: 18 September 2015
Published online: 23 September 2015

References

1. Perkins D, Gu H, Boteva K, Lieberman J. Relationship between duration of untreated psychosis and outcome in first episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005;162:1785–804.
2. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first episode patients. Arch Gen Psychiatry. 2005;62:975–83.
3. Norman RM, Lewis SW, Marshall M. Duration of untreated psychosis and its relationship to clinical outcome. Br J Psychiatry. 2005;187(Suppl):19–23.
4. Skeate A, Jackson C, Birchwood M, Jones C. Duration of untreated psychosisand pathways to care in first-episode psychosis. Investigation of help-seekingbehaviour in primary care. Br J Psychiatry Suppl. 2002;43:s73–7.
5. Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry. 2001;50:884–97.
6. Häfner H, Nowotny B, Löffler W, an der Heiden W, Maurer K. When and how does schizophrenia produce social deficits? Eur Arch Psychiatry Clin Neurosci. 1995;246:17–28.
7. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet. 2003;25(361):281–8.
8. Department of Health. Mental Health Policy Implementation Guide. Department of Health, 2001. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_4009350.
9. Lin A, Nelson B, Yung AR. Editorial: 'At-risk' for psychosis research: where are we heading? Epidemiol Psychiatr Sci. 2012;21(4):329–34.
10. McGorry PD, Killackey E, Yung A. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry. 2008;7(3):148–56.
11. Joa I, Johannessen JO, Langeveld J, Friis S, Melle I, Opjordsmoen S, et al. Baseline profiles of adolescent vs. adult-onset first-episode psychosis in an early detection program. Acta Psychiatr Scand. 2009;119(6):494–500.
12. Simon A, Lester HE, Tait L, Stip E, Roy P, Conrad G, et al. The International Study on General Practitioners and Early Psychosis (IGPS). Schizophr Res. 2009;108:182–90.
13. Potts Y, Gillies ML, Wood SF. Lack of mental well-being in 15 year-olds: an undisclosed iceberg? Fam Pract. 2001;18:95–100.
14. Joa I, Johannessen JO, Auestad B, Friis S, McGlashan T, Melle I, et al. The key to reducing duration of untreated first psychosis: Information campaigns. Schizophr Bull. 2008;34:466–72.
15. Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S, et al. Early detection strategies for untreated first episode psychosis. Schizophr Res. 2001;51(1):39–46.
16. Langeveld J, Joa I, Larsen TK, Rennan AJ, Cosmovici EM, Johannessen JO. Teachers' awareness for psychotic symptoms in secondary school: The effects of an early detection programme and information campaign. Early Interv Psychiatry. 2011;5:115–21.
17. Askell-Williams H, Lawson MJ, Murray-Harvey R. Teaching and learning about mental illnesses: an Australian perspective. Int J Ment Health Promot. 2007;9:26–36.
18. Peterson FL, Cooper R, Laird J. Enhancing teachers health literacy in school health promotion: a vision for the new millennium. J Sch Health. 2001;71:138–44.

19. Lloyd-Evans B, Crosby M, Stockton S, Pilling S, Hobbs L, Hinton M, et al. Initiatives to shorten duration of untreated psychosis: systematic review. Br J Psychiatry. 2011;198(4):256–63.
20. Collins A, Holmshaw J. Early detection - A survey of secondary school teachers knowledge about psychosis. Early Interv Psychiatry. 2008;2(2):90–7.
21. Masillo A, Monducci E, Pucci D, Telesforo L, Battaglia C, Carlotto A, et al. Evaluation of secondary school teachers' knowledge about psychosis: a contribution to early detection. Early Interv Psychiatry. 2012;6:76–82.
22. Foy R, Francis JJ, Johnston M, Eccles MP, Lecouturier J, Bamford C, et al. The development of a theory-based intervention to promote appropriate disclosure of a diagnosis of dementia. BioMed Central Health Services Research. 2007;7:207. doi:10.1186/1472-6963-7-207.
23. Michie S, Prestwich A. Are interventions theory-based? Development of a theory coding scheme. Health Psychol. 2010;29:1–8.
24. Eccles M. The Improved Clinical Effectiveness through Behavioral Research Group (ICEBeRG). Designing theoretically-informed implementation interventions Implementation Science. 2006;1:4. doi:10.1186/1748-5908-1-4.
25. Ajzen I. From intentions to action: A theory of planned behavior. In: Kuhl J, Beckman J, editors. In *Action control: From cognitions to behaviors*. New York: Springer; 1985. p. 11–39.
26. Ajzen I. The theory of planned behavior. Organ Behav Hum Dec. 1991;50:179–211.
27. Skår S, Sniehotta FF, Araujo-Soares V, Molloy GJ. Prediction of behaviour vs. prediction of behaviour change: The role of motivational moderators in the theory of planned behaviour. Appl Psychol-Int Rev. 2008;57:609–27.
28. Sandberg T, Conner M. Anticipated regret as an additional predictor in the theory of planned behaviour: A meta-analysis. Br J Soc Psychol. 2008;47(4):589–606.
29. Conner M, Sparks P: Theory of Planned Behaviour and Health Behaviour. In *Predicting health behaviour: Research and practice with social cognition models*. 2nd edition. Edited by Conner M, Sparks P. Mainhead: Open University Press; 2005:170–222.
30. Ajzen I, Madden TJ. Prediction of goal-directed behavior: Attitudes, intentions, and perceived behavioral control. JESP. 1986;22:453–74.
31. Armitage CJ, Conner M. Efficacy of the theory of planned behavior: a meta-analytic review. Br J Soc Psychol. 2001;40:471–99.
32. Martin JJ, Kulinna PH. Self-Efficacy Theory and theTheory of Planned Behavior: Teaching Physically Active Physical Education Classes. Res Q Exerc Sport. 2004;75(3):288–97.
33. Jeong M, Block ME. Physical education teachers' beliefs and intentions toward teaching students with disabilities. Initiatives to shorten duration of untreated psychosis: systematic review. Res Q Exerc Sport. 2011;82(2):239–46.
34. Lee, J.-y: Predictors of Teachers' Intention to Refer Students With ADHD to Mental Health Professionals: Comparison of U.S. and South Korea. *School Psychol Quart* 2013, Advance online publication. doi: 10.1037/spq0000046.
35. Ajzen I: Constructing a TpB Questionnaire: Conceptual and Methodological Considerations [http://www.uni-bielefeld.de/ikg/zick/ajzen%20construction%20a%20tpb%20questionnaire.pdf].
36. Francis JJ, Eccles MP, Johnston M, Walker A, Grimshaw J, Foy R, Kaner EFS, Smith L, Bonetti D: Constructing questionnaires based on the theory of planned behaviour. A manual for health services researchers [http://openaccess.city.ac.uk/1735/].
37. Samejima F. Estimation of latent ability using a response pattern of graded scores. Psychometrika Monograph Supplement. 1969;34:100–14.
38. Conner M, Kirk S, Cade J, Barrett J. Why do women use dietary supplements? The use of the theory of planned behavior to explore beliefs about their use. Soc Sci Med. 2001;52:621–33.
39. Brown TA. Confirmatory factor analysis for applied research. New York: Guilford Press; 2006.
40. Wolfle LM. The introduction of path analysis to the social sciences, and some emergent themes: An annotated bibliography. Struct Equ Model. 2003;10(1):1–34.
41. Hintze J. NCSS (version 7.1). Kaysville, UT: CSS, LLC; 2008.
42. Muthén LK, Muthén BO. Mplus: Statistical Analysis With Latent Variables (Version 6.1). Los Angeles, CA, 1998–2010. https://www.statmodel.com/download/usersguide/Mplus%20Users%20Guide%20v6.pdf.
43. Francis J, Eccles M, Johnston M, Whitty P, Grimshaw JM, Kaner EF, et al. Explaining the effects of an intervention designed to promote evidence-based diabetes care: a theory-based process evaluation of a pragmatic cluster randomised controlled trial. Implement Sci. 2008;3:50. doi:10.1186/1748-5908-3-50.
44. Cortina JM. What is coefficient alpha? An examination of theory and applications. J Appl Psychol. 1993;78:98–104.
45. Ajzen I. Perceived behavioral control, self-efficacy, locus of control, and the theory of planned behavior. J Appl Soc Psychol. 2002;32:665–83.
46. Pas ET, Bradshaw CP, Hershfeldt PA, Leaf PJ. A multilevel exploration of the influence of teacher efficacy and burnout on response to student problem behavior and schoolbased service use. School Psychol Quart. 2010;25:13–27. doi:10.1037/a0018576.
47. Sparks P, Guthrie CA, Shepherd R. The dimensional structure of the perceived behavioral control construct. J Appl Psychol. 1997;27:418–38.
48. French DP, Cooke R, McLean N, Williams M, Sutton S. What do people think about when they answer theory of planned behaviour questionnaires? A "think aloud" study. J Health Psychol. 2007;12:672–68.
49. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Increasing response rates to postal questionnaires: systematic review. BMJ. 2002;324:1183.
50. Crowne DP, Marlowe D. A new scale of social desirability independent of pschopathology. J Consult Psychol. 1960;24:349–54.
51. Armitage CJ, Conner M. Predictive validity of the theory of planned behavior: The role of questionnaire format and social desirability. J Community Appl Socl Psychol. 1999;9:261–72.

Submit your next manuscript to BioMed Central and take full advantage of:

- **Convenient online submission**
- **Thorough peer review**
- **No space constraints or color figure charges**
- **Immediate publication on acceptance**
- **Inclusion in PubMed, CAS, Scopus and Google Scholar**
- **Research which is freely available for redistribution**

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

© 2015 Russo *et al.* Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Appendix 9 Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis

Schizophrenia Research 148 (2013) 175–180

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis ☆

Christy Hui [a,b], Carmen Morcillo [a,c], Debra A. Russo [a,c], Jan Stochl [a,c], Gillian F. Shelley [c], Michelle Painter [c], Peter B. Jones [a,c,d], Jesus Perez [a,c,*]

[a] Department of Psychiatry, University of Cambridge, Cambridge, UK
[b] Department of Psychiatry, University of Hong Kong, Hong Kong, China
[c] CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, UK
[d] NIHR Collaboration for Leadership in Applied Health Research & Care, Cambridge, UK

ARTICLE INFO

Article history:
Received 7 March 2013
Received in revised form 29 April 2013
Accepted 23 May 2013
Available online 14 June 2013

Keywords:
At-risk-mental-state
Early intervention
High-risk
Psychosis
Psychotic-like
Schizophrenia

ABSTRACT

Objective: Recent studies suggest that psychotic-like experiences may also act as markers for non-psychotic psychiatric disorders, which may indicate that the focus of research in individuals at high risk (HR) for psychosis needs updating. In this study we thoroughly examined the clinical and functional characteristics of a consecutive cohort of young people at HR for psychosis and compared them to a matched sample of healthy volunteers.

Method: Between February 2010 and September 2012 60 help-seeking HR individuals, aged 16–35, were recruited from CAMEO Early Intervention in Psychosis Service, Cambridgeshire, UK. Forty-five age- and gender-matched healthy volunteers were randomly recruited from the same geographical area. Sociodemographic, psychiatric morbidity, functioning and quality of life measures were compared between both groups.

Results: HR individuals suffered a wide range of DSM-IV psychiatric disorders, mainly within the affective and anxiety diagnostic spectra. In comparison to healthy volunteers, young people at HR reported more suicidal ideation/intention, depressive and anxiety symptoms and presented with remarkably poor functioning and quality of life.

Conclusion: The presence of co-morbid moderate or severe depressive and anxiety symptoms was common in our sample of young people at enhanced risk for psychosis. A HR mental state may be associated not only with an increased risk for psychosis, but also other psychiatric disorders. Our findings may have implications for the future implementation of therapeutic interventions that this population could benefit from.

© 2013 The Authors. Published by Elsevier B.V. All rights reserved.

1. Introduction

There has been a decline in transition rates into psychosis in cohorts of individuals at high risk (HR) of developing psychosis across different centres worldwide, over the last few years (Yung et al., 2007). Different psychological and pharmacological interventions have not significantly reduced transitions in recent randomised controlled trials (McGorry et al., 2012; Morrison et al., 2012). This may suggest that the focus of research in this population group needs updating.

Growing evidence is indicating that psychosis may lie on a continuum, with mild psychotic symptoms or psychotic-like experiences at one end and schizophrenia and related psychotic disorders at the other (Kendler et al., 1996; van Os et al., 2001; Dhossche et al., 2002; Johns et al., 2004; van Os et al., 2009). Recent studies including population-based samples also suggest that nearly 80% of the adolescents who report psychotic-like symptoms may have at least one other psychiatric disorder (Kelleher et al., 2012a, 2012b). Furthermore, co-presence of psychotic symptoms in adolescents and young adults with disorders of anxiety and depression appears to be more prevalent than previously considered, and an etiological and functionally relevant feature (Wigman et al., 2012).

Psychotic experiences may also act as markers for non-psychotic psychiatric disorders in individuals at clinical HR for psychosis. Fusar-Poli et al. (2012) found that 73% of the HR individuals recruited

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory, Version II; BLIPS, Brief Limited Intermittent Psychotic Symptoms; CAARMS, Comprehensive Assessment of At-Risk-Mental-States; FEP, First-Episode Psychosis; GAF, Global Assessment of Functioning; HR, High Risk; MANSA, Manchester Short Assessment of Quality of Life; MINI, Mini International Neuropsychiatric Interview; PAF, Postcode Address File; PANSS, Positive and Negative Syndrome Scale; YBOCS, Yale-Brown Obsessive Compulsive Symptoms Scale; YMRS, Young Mania Rating Scale.

☆ This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

* Corresponding author at: Block 7, Ida Darwin Site, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EE, UK. Tel.: +44 1223884360; fax: +44 1223884362.
E-mail address: jp440@cam.ac.uk (J. Perez).

0920-9964/$ – see front matter © 2013 The Authors. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.05.026

© 2013 The Authors. Published by Elsevier B.V. All rights reserved

to their study (n = 509) had at least one Axis I comorbid diagnosis, with major depression as predominant diagnosis, followed by anxiety disorders. Similarly, Salokangas et al. (2012) identified comorbid psychiatric disorders in almost 80% of their HR sample (n = 245).

It is therefore important to thoroughly understand the type and severity of psychopathology in people at HR for psychosis in order to develop specific care pathways and interventions that this group could likely benefit from. To achieve this goal, comparisons with healthy volunteers to evaluate the overall psychiatric morbidity and subsequent impact on quality of life and functioning in HR individuals are highly recommended. It is noteworthy that these comparisons are still very limited in the current scientific literature, with only a handful of studies assessing the real impact of HR mental states on functioning and quality of life (Velthorst et al., 2010; Granö et al., 2011; Fusar-Poli et al., 2012).

The aims of this study were to further delineate the clinical manifestations of young people at HR for psychosis at the time of their referral to mental health services and evaluate their level of global functioning, occupational status and quality of life in comparison to a sample of healthy volunteers recruited from the same geographical area.

2. Methods

We compared demographic, psychiatric morbidity, functioning and quality of life measures between help-seeking HR individuals and healthy volunteers recruited from Cambridgeshire, UK.

2.1. Setting

CAMEO (http://www.cameo.nhs.uk) is an early intervention service in psychosis which offers management for people aged 14–35 years suffering from first-episode psychosis (FEP) in Cambridgeshire, UK. CAMEO also accepts referrals of people at HR aged 16–35. Referrals are accepted from multiple sources including general practitioners, other mental health services, school and college counsellors, relatives and self-referrals (Cheng et al., 2011).

2.2. Sample

A consecutive cohort of 60 help-seeking individuals, aged 16–35, referred to CAMEO Early Intervention in Psychosis Service from February 2010 to September 2012 met criteria for HR, according to the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2005). From this assessment, HR individuals were divided into three groups based on whether they were mainly characterised by: i) vulnerability traits (family history of psychosis in first degree relative plus significant drop in functioning levels within past 12 months), ii) attenuated psychotic symptoms, or iii) brief limited intermittent psychotic symptoms (BLIPS). In our sample, all individuals fulfilled criteria for the attenuated psychotic symptoms' group. Seven individuals (11.7%) also qualified for the vulnerability traits' group. Intake exclusion criteria included: i) acute intoxication or withdrawal associated with drug or alcohol abuse or any delirium, ii) confirmed intellectual disability (Wechsler Adult Intelligence Scale — tested IQ <70), or iii) prior total treatment with antipsychotics for more than one week.

During the same period (February 2010–September 2012), a random sample of 45 healthy volunteers was recruited by post, using the Postcode Address File (PAF®) provided by Royal Mail, UK. Healthy volunteers interested in the study could only participate if they were aged 16–35, resided in the same geographical area as HR participants (Cambridgeshire), and did not have previous contact with mental health services. They were recruited for the exclusive purpose of this research.

2.3. Ethical approval

Ethical approval was granted by the Cambridgeshire East Research Ethics Committee.

2.4. Measures

All participants were assessed with sociodemographic (age, gender, ethnicity, education level, marital status, and living accommodation), psychiatric morbidity, functioning and quality of life measures at the time of their referral to CAMEO. The assessments were carried out by senior research clinicians trained in each of the measurement tools. HR participants were also interviewed by senior trained psychiatrists working in CAMEO, using the Mini International Neuropsychiatric Interview (MINI), Version 6.0.0, a brief structured diagnostic interview for DSM-IV Axis I psychiatric disorders (Sheehan et al., 1998).

The Positive and Negative Syndrome Scale (PANSS) for psychotic symptoms was employed to capture the severity of positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items) in a 7-point scale, with higher scores indicating greater severity of illness (Kay et al., 1987). Summary score and sub-domain scores of positive, negative and general psychopathology symptoms were computed.

The Beck Depression Inventory Version II (BDI-II) (Beck et al., 1996) and the Beck Anxiety Inventory (BAI) (Beck et al., 1988) were used to assess depressive and anxiety symptoms respectively. The BDI-II is a widely used self-complete instrument to assess depressive symptom severity in the past two weeks. It consists of 21 items rated on a 4-point scale from absent (0), mild (1), moderate (2) to severe (3). In addition to item scores, a composite score (range 0–63 points) was calculated by summing individual items in the BDI-II. The composite score was used to further divide participants into 4 groups in which scores of 0–13 indicates minimally depressed, 14–19 mildly depressed, 20–28 moderately depressed and 29–63 severely depressed (Dolle et al., 2012). For the purpose of this study, the BDI-II item 9 on current suicidal thoughts or wishes was used to categorize subjects into absent (scoring 0) or present (scoring 1–3) suicidal ideation. Likewise, the BAI is a 21-item self-complete measure of anxiety symptoms also rated on a 4-point scale, from 0 indicating absent to 3 indicating severe. Individual item scores and composite score (range 0–63) were computed. Participants were further divided into 4 groups according to their BAI composite score: scores of 0–7 indicates minimal anxiety, 8–14 mild anxiety, 16–25 moderate anxiety, and 26–63 severe anxiety (Beck and Steer, 1993).

Manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al, 1978). The scale has 11 items — while 7 items on elevated mood, increased motor activity–energy, sexual interest, sleep, language–thought disorder, appearance and insight were rated from 0 (absence) to 4 (severe), the remaining 4 items on irritability, speech, content and disruptive–aggressive behaviour were rated from 0 (absent) to 8 (severe). A summary score of all the items of the YMRS was calculated (range 0–60).

The Yale–Brown Obsessive Compulsive Symptom Checklist and Severity Scales (YBOCS) (Goodman et al., 1989) were used to examine the presence and severity of obsessions and compulsions. The proportion of subjects having obsessions and/or compulsions in each group was calculated. For those who had at least one obsession and/or compulsion, the mean total severity scores were also generated.

The Global Assessment of Functioning (GAF) is a commonly used functioning scale in psychiatric research (Hall, 1995). The GAF assesses global functioning in the past month. Both symptoms and disability dimensions were assessed using an impression score of 1 to 100, with 10 points separating each level (Endicott et al., 1976), and lower scores representing higher severity of symptoms and poorer level of functioning respectively. Occupational status was also recorded.

Quality of life was assessed using the Manchester Short Assessment of Quality of Life (MANSA) (Priebe et al., 1999). The subjective and objective dimensions of quality of life were captured. For the purpose of this study, the subjective dimension comprising of the following domains was analysed: life in general, health, work and education, finance, leisure, safety, living situation, social and family relations. Each item is rated from 1 (worst) to 7 (best possible satisfaction). The overall mean subjective quality of life score was computed by averaging all the items in the subjective dimension (Eklund, 2009).

2.5. Statistical analysis

All analyses were performed using version 20 of SPSS (SPSS, Inc., Chicago, Illinois). We compared sociodemographic information between HR individuals and healthy volunteers. Clinical morbidity measures including PANSS, BDI-II, BAI, YMRS and YBOCS, functioning measures including GAF and occupational status, as well as subjective quality of life measured by MANSA were further compared between the two groups. All comparisons were made using chi-square test or Fisher's exact test for categorical variables and *t*-test or Mann–Whitney *U* test for continuous variables. A p-value of less than 0.05 represents a significant difference.

3. Results

3.1. Sociodemographic profile

The whole study population had a mean age of 20.7 years (SD = 3.4). Gender was nearly evenly split between male (n = 55; 52.4%) and female (n = 50; 47.6%). Table 1 compares the basic demographics between HR individuals and healthy volunteers. Both groups did not differ in age, gender, ethnicity and current accommodation type. Less HR individuals achieved higher education degrees (p = 0.001) compared to healthy volunteers, and more HR individuals were single (p = 0.033). A significant proportion of HR individuals were on antidepressant or/and anxiolytic medication (41.7%) at the time of their first contact with CAMEO.

Table 1
Sociodemographic comparison between HR individuals and healthy volunteers.

Sociodemographic characteristics[†]	HR (n = 60)	HV (n = 45)	p-Value
Age at study entry, years, mean (SD)	20.2 (2.9)	21.4 (3.9)	0.088[a]
Gender, male, n (%)	31 (51.7)	24 (53.3)	0.866[b]
Ethnicity, n (%)[‡]			
White	56 (93.3)	41 (91.1)	0.722[c]
Mixed	2 (3.3)	3 (6.7)	0.649[c]
Asian	1 (1.7)	1 (2.2)	1.000[c]
Black	1 (1.7)	0 (0)	1.000[c]
Education level, n (%) (9)			
Primary	5 (9.8)	0 (0)	0.058[c]
Secondary	26 (51.0)	10 (22.7)	0.006[c]
Further[§]	17 (33.3)	20 (45.5)	0.298[c]
Higher	3 (5.9)	15 (31.8)	0.001[c]
Marital status, n (%) (7)			
Single	48 (90.6)	33 (73.3)	0.033[c]
Married/co-habiting	5 (9.4)	11 (24.4)	0.057[c]
Divorced/dissolved	0 (0)	1 (2.2)	0.459[c]
Current accommodation type, n (%) (6)			
Detached house	13 (24.1)	15 (33.3)	0.372[c]
Semi-detached house	18 (33.3)	10 (22.2)	0.266[c]
Terraced house	12 (22.2)	12 (26.7)	0.644[c]
Flat	4 (7.4)	7 (15.6)	0.219[c]
Bedsit/studio	1 (1.9)	0 (0)	1.000[c]
Communal establishment	6 (11.1)	1 (2.2)	0.123[c]
Current psychiatric medication, n (%)	25 (41.7)	0 (0)	<0.00[b]
Current psychiatric medication type, n (%)[*]			
Antipsychotics	0 (0)	0 (0)	–
Antidepressants	24 (38.3)	0 (0)	<0.001[c]
Anxiolytics	2 (1.7)	0 (0)	0.505[c]
Both antidepressants and anxiolytics	1 (1.7)	0 (0)	1.000[c]

HR = high risk; HV = healthy volunteers; SD = standard deviation; n = number.
[†]Number of missing observations in brackets.
[‡]'White ethnicity' refers to subjects who are White British, White Irish, or other White backgrounds. 'Mixed ethnicity' refers to those who are White and Black Caribbean, mixed White and Black African, mixed White and Asian, or any other mixed backgrounds. 'Asian ethnicity' refers to those who are Indian or Chinese. 'Black ethnicity' refers to subject from any Black backgrounds.
[§]UK National Vocational Qualifications (NVQs) or A-Levels.
[*]Multiple answers were allowed for those who had any psychiatric medication taken during study entry.
[a] Independent *t*-test.
[b] Chi-square test.
[c] Fisher's exact test.

3.2. Psychiatric morbidity

We obtained MINI DSM-IV diagnoses for 55 of the 60 HR individuals. 38 (69.1%) had more than one DSM-IV psychiatric diagnosis, mainly within the affective and anxiety diagnostic spectra. Primary diagnoses for this group were ranked as follows: major depressive episode, current or recurrent (n = 26; 47.3%) > social phobia (n = 7; 12.7%) = generalised anxiety disorder (n = 7; 12.7%) > obsessive compulsive disorder (n = 5; 9.1%) > bipolar disorder, type II (n = 2; 3.6%) > panic disorder (n = 1; 1.8%) = posttraumatic stress disorder (n = 1; 1.8%). Six HR individuals (10.9%) did not fulfil enough criteria for a DSM-IV Axis I diagnosis.

Table 2 shows that HR individuals had higher scores (i.e., greater symptom severity) in total PANSS and all its sub-domains, including positive, negative and general psychopathology symptoms compared with healthy volunteers (all with p < 0.001). However, all scores suggested a "mildly ill" group with regard to psychotic symptoms (Leucht et al., 2005).

HR individuals also had a higher total BDI-II score (i.e., more depressed) than controls (29.9 ± 12.8 vs. 5.6 ± 5.5, p < 0.001). This difference was significant in all items. We further divided participants into 4 groups according to their total scores in BDI-II. HR individuals were significantly more likely to be severely or moderately depressed (54.0% vs. 0%, p < 0.001 and 20.0% vs. 4.5%, p = 0.025, respectively). We tested if HR individuals who were currently on antidepressants (n = 24) had a higher baseline BDI-II score than those who were not on antidepressants (n = 36). However, no difference on the means of BDI-II sum scores was observed between the two groups (32.7 ± 12.4 vs. 27.8 ± 13.0, p = 0.184). HR individuals had a 72.0% endorsement in suicidal thoughts or intention, as measured with item 9 of BDI-II, whereas only 9.1% of healthy volunteers had positive response in this item (p < 0.001).

Similarly, BAI scores showed that HR individuals had more anxiety symptoms (28.2 ± 11.9 vs. 6.7 ± 5.6, p < 0.001). Indeed, 41 HR individuals (85.4%) suffered moderate or severe anxiety symptoms.

Although HR individuals had a significant higher YMRS score than healthy volunteers (p < 0.001), the mean score was 3.9 (SD = 4.1), suggesting subclinical severity.

Approximately 80% of HR individuals had experienced at least one obsessive symptom. Among those who had any obsession or compulsion, the mean of YBOCS total severity score was significantly higher in HR individuals than healthy volunteers (20.1 ± 5.8 vs. 5.3 ± 1.5, p < 0.001), suggesting moderate and subclinical severity respectively.

3.3. Transitions from HR to FEP

After more than one year of follow-up for each individual at HR in our sample, only 6 (10%) made a transition into FEP. We obtained MINI DSM-IV diagnoses at baseline for 5 of them. 4 had an initial diagnosis of major depression, current or recurrent, and one did not fulfil enough criteria for a DSM-IV mental disorder. None of the HR individuals from this cohort received antipsychotics during the follow-up

© 2013 The Authors. Published by Elsevier B.V. All rights reserved

Table 2
Clinical comparison between HR individuals and healthy volunteers.

Clinical characteristics[†]	HR (n = 60)	HV (n = 45)	p-Value
PANSS, mean (SD) (6)			
Positive	13.1 (3.2)	7.1 (0.5)	<0.001[a]
Negative	12.4 (5.0)	7.8 (0.9)	<0.001[a]
General psychopathology	32.7 (7.0)	16.3 (1.3)	<0.001[a]
Sum of all items	58.2 (12.1)	31.3 (1.9)	<0.001[a]
BDI-II (11)			
Sum of all items, mean (SD)	29.9 (12.8)	5.6 (5.5)	<0.001[a]
Suicidality (score 1–3), n (%)	36 (72.0)	4 (9.1)	<0.001[b]
Depression subgroup, n (%)			<0.001[b]
Minimal (score 0–13)	5 (10.0)	39 (88.6)	<0.001[b]
Mild (score 14–19)	8 (16.0)	3 (6.8)	0.167[b]
Moderate (score 20–28)	10 (20.0)	2 (4.5)	0.025[b]
Severe (score 29–63)	27 (54.0)	0 (0)	<0.001[b]
BAI (15)			
Sum of all items, mean (SD)	28.2 (11.9)	6.7 (5.6)	<0.001[a]
Anxiety subgroup, n (%)			<0.001[b]
Minimal (score 0–7)	2 (4.2)	29 (67.4)	<0.001[b]
Mild (score 8–15)	5 (10.4)	9 (20.9)	0.165[b]
Moderate (score 16–25)	12 (25.0)	5 (11.6)	0.102[b]
Severe (score 26–63)	29 (60.4)	0 (0)	<0.001[b]
YMRS (7)			
Sum of all items, mean (SD)	3.9 (4.1)	0.5 (1.2)	0.001[a]
YBOCS (13)			
Having obsession, n (%)	37 (77.1)	2 (4.5)	<0.001[b]
Having compulsion, n (%)	34 (70.8)	1 (2.3)	<0.001[b]
Sum of all items, mean (SD)	20.1 (5.8)	5.3 (1.5)	<0.001[a]
Severity subgroups, n (%)			<0.001[b]
Subclinical (score 0–7)	2 (5.4)	3 (100)	0.001[c]
Mild (score 8–15)	5 (13.5)	0 (0)	0.001[c]
Moderate (score 16–23)	20 (54.1)	0 (0)	0.231[c]
Severe (score 24–31)	9 (24.3)	0 (0)	1.000[c]
Extreme (score 32–40)	1 (2.7)	0 (0)	1.000[c]

HR = high risk; HV = healthy controls; SD = standard deviation; n = number; PANSS = Positive and Negative Syndrome Scale, BDI-II = Beck Depression Inventory, Version II, BAI = Beck Anxiety Inventory, YMRS = Young Mania Rating Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.
[†]Number of missing observations in brackets.
[a] Independent *t*-test.
[b] Chi-square test.
[c] Fisher's exact test.

Table 3
Functioning and quality of life comparison between HR individuals and healthy volunteers.

Functioning and quality of life measures[†]	HR (n = 60)	HV (n = 45)	p-Value
GAF, mean (SD) (3)			
Symptoms	45.4 (8.9)	86.6 (3.8)	<0.001[a]
Disability	48.6 (9.4)	86.7 (3.6)	<0.001[a]
Occupational status, n (%) (7)[‡]			0.061[b]
Unemployed	20 (37.7)	8 (17.8)	0.029[b]
Employed	16 (30.2)	22 (48.9)	0.058[b]
Students	17 (32.1)	15 (33.3)	0.895[b]
MANSA, mean (SD) (11)	3.8 (1.0)	5.6 (0.6)	<0.001[c]
Life as a whole today	3.4 (1.5)	5.6 (1.0)	0.001[c]
Health	3.5 (1.4)	5.4 (1.1)	<0.001[c]
Present mental health	3.0 (1.4)	6.2 (0.8)	<0.001[c]
Job (if working)	4.1 (1.8)	5.4 (1.4)	0.011[c]
Not working (if not working)	3.7 (1.7)	4.0 (1.9)	0.532[c]
Financial situation	3.5 (1.5)	4.6 (1.5)	0.001[c]
Leisure activities	3.9 (1.9)	5.6 (1.3)	<0.001[c]
Number of friends	4.2 (1.8)	5.8 (1.0)	<0.001[c]
Relationships with friends	4.5 (1.7)	5.7 (0.9)	<0.001[c]
Personal safety	4.0 (1.6)	5.8 (0.9)	<0.001[c]
Accommodation	4.6 (1.7)	6.0 (1.2)	<0.001[c]
People one live with (if living with other)	4.7 (1.4)	6.1 (0.9)	<0.001[c]
Living alone (if living alone)	4.0 (–)	–	–
Relationship with family	4.0 (1.4)	5.6 (1.0)	<0.001[c]
Life overall	3.0 (1.4)	5.8 (0.9)	<0.001[c]

HR = high risk; HV = healthy controls; SD = standard deviation; n = number; GAF = Global Assessment of Functioning; MANSA = Manchester Short Assessment of Quality of Life.
[†]Number of missing observations in brackets.
[‡]Employment status is broadly categorized into 3 groups. 'Unemployed' includes subjects who do not have a job, either they are looking for work, not looking for work (e.g., housewife), or not being able to work due to medical reasons. 'Employed' refers to people who have full/part-time employment, or employed but currently unable to work. 'Students' refer to full/part-time students.
[a] Mann–Whitney *U* test.
[b] Chi-square test.
[c] Independent *t*-test.

period, but they were treated with other psychiatric medications, i.e. anxiolytics and/or antidepressants, if clinically required.

3.4. Functioning and quality of life

Table 3 compares functioning, employment status, and quality of life between HR and healthy individuals. HR subjects had poorer functioning, with much lower scores in GAF symptoms and disability than healthy volunteers (45.4 ± 8.9 vs. 86.6 ± 3.8 and 48.6 ± 9.4 vs. 86.7 ± 3.6, respectively, both with $p < 0.001$), suggesting that individuals with HR mental states suffered serious psychiatric symptoms and any serious impairment in social, occupational or academic functioning. Higher unemployment rate was found in the HR group (37.7% vs. 17.8%, $p = 0.029$). HR individuals also reported poorer quality of life (3.8 ± 1.0 vs. 5.6 ± 0.6, $p < 0.001$).

4. Discussion

This study compared psychiatric morbidity, functioning and quality of life between 60 young people at HR for psychosis at the time of their referral to CAMEO and 45 healthy volunteers. Overall, our findings indicate that, beyond psychotic symptoms, there are many other psychopathological conditions that may be interfering in the global functioning of those at HR. More specifically, our study showed that HR individuals i) suffered a wide range of psychiatric disorders and mild psychotic symptoms, ii) reported more suicidal ideation/intention, depressive and anxiety symptoms, and iii) presented with worse levels of functioning, quality of life and employment status than healthy volunteers.

These results are in line with previous evidence suggesting a significant association between HR mental states and several other psychiatric disorders (Fusar-Poli et al., 2012; Salokangas et al., 2012). We found that almost 70% of HR individuals in our sample had more than one DSM-IV Axis I diagnosis. In particular, HR individuals had a statistically significant higher prevalence of moderate/severe depression, anxiety, obsessive–compulsive behaviours, and suicidality than healthy volunteers.

Our results suggest that individuals at HR are a heterogeneous group which tends to present with more than one psychiatric disorder, mainly depression and/or anxiety-related. Suicidal ideation and intention were also very prevalent in our HR cohort. Previous studies have reported similar enhanced risk of suicide in population-based and clinical samples (Preti et al., 2009; Hutton et al., 2011; Kelleher et al., 2012a, 2012b). This could be related to a variety of factors, such as comorbid psychiatric disorders (DeVylder et al., 2012), distress associated with psychotic-like experiences or mild psychotic symptoms, especially auditory hallucinations (Lataster et al., 2010), and mood variability (Palmier-Claus et al., 2012).

Recent studies, both in adolescent and adult populations, have already shown a strong relationship between HR for psychosis and presence of comorbid mood and anxiety disorders (Kelleher et al., 2012a, 2012b; Wigman et al., 2012). These associations might be even stronger at earlier stages of development, where psychotic experiences among young adolescents appear to follow a dose–response pattern in the prediction of a wide variety of future psychopathology (Kelleher et al., 2012a, 2012b). Interestingly, in contrast with previous findings that described a direct relationship between the degree of psychotic symptoms

and comorbid psychiatric disorders in young people, individuals at clinical HR in our sample were affected by mild psychotic symptoms.

Our findings highlight the lack of specificity and predictive value of psychotic symptoms and carry important implications for clinicians and researchers in the field of psychosis. Psychotic experiences appear to be common, not only among those patients who suffer from a psychotic illness, but also from other disorders such as depression and anxiety (Wigman et al., 2012). Although the causal mechanisms of this association are not well understood, it has been hypothesized that a HR mental state may be an indicative marker of risk for multiple psychiatric disorders (Kelleher et al., 2012a, 2012b). During childhood and adolescence, clinical phenotypes of different psychiatric disorders might overlap, reaching a greater differentiation throughout adulthood (Kim-Cohen et al., 2003; Jones, 2013). Also, traumatic events in childhood could eventually manifest as psychotic-like symptoms in the context of non-psychotic psychiatric disorders (Kelleher et al., 2013). Therefore, psychotic and non-psychotic disorders may share similar risk factors and these could have an impact on neurodevelopmental processes that may involve genetic, structural and/or neurobiological changes, resulting in different psychiatric syndromes (Jacobson et al., 2010; Alemany et al., 2011; Murray and Jones, 2012). It is also possible that mild psychotic symptoms experienced by HR individuals may contribute to the development of other psychiatric disorders.

Notably, people at HR in our and other samples (Bechdolf et al., 2005; Fusar-Poli et al., 2012; Zimbrón et al., 2012) endorsed a remarkably poor global functioning and quality of life, which was particularly striking when we compared them to healthy volunteers from the same region. This would justify special attention from mental health services in order to develop appropriate care pathways for a population also characterised by a significant risk of suicidality, regardless of current uncertainties on the mechanisms underlying these presentations. On the basis of our findings, clinical interventions in individuals at HR indentified in early intervention in psychosis services should aim at targeting a broader range of psychopathology, especially mood and anxiety symptoms, rather than just focusing on the treatment and/or prevention of psychosis.

4.1. Limitations

One of the limitations of the study is its cross-sectional nature, where causal inferences on the HR state, psychiatric morbidity and impaired functioning cannot be made. Efforts to follow-up this HR cohort are being undertaken in order to assess if HR mental states are associated with the development of functional difficulties and psychiatric morbidity. Also, the study only included people aged 16–35 years, which might affect the generalisability of our results. However, this is a valuable homogenous cohort with all individuals mainly suffering from attenuated psychotic symptoms. Furthermore, we did not match the study groups on educational level, yet the groups did not differ with respect to age, gender and ethnicity. Finally, we did not include a chronicity criterion to determine whether people with longer duration of HR mental state criteria had a different profile of psychopathology from those with shorter duration.

Funding body agreements and policies

The authors acknowledge funding support from NIHR programme grant RP-PG-0606-1335 'Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses' awarded to PBJ. The work forms part of the NIHR Collaboration for Leadership in Applied Health Research & Care for Cambridgeshire & Peterborough (CLAHRC-CP). The NIHR had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

PBJ is the chief investigator for the research programme that this study is part of. JP and MP are principal investigator and project manager, respectively. All the authors participated in the design and implementation of the study. CH, CM and JP drafted the manuscript. Statistical analyses were carried out by CH and JS. All the authors provided a critical review and final approval of the manuscript.

Conflict of interest

The authors have not transmitted any conflicts of interest based on business relationships of their own or of immediate family members.

Acknowledgements

The authors thank the PAATh Study team (Erica Jackson, Chris McAlinden, Carolyn Crane and Gerhard Smith) and all the members of CAMEO services for their help and support in the elaboration of this study.

References

Alemany, S., Arias, B., Aguilera, M., Villa, H., Moya, J., Ibáñez, M.I., Vossen, H., Gastó, C., Ortet, G., Fañanás, L., 2011. Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. Br. J. Psychiatry 199 (1), 38–42.

Bechdolf, A., Pukrop, R., Kohn, D., Tschinkel, S., Veith, V., Schultze-Lutter, F., Ruhrmann, S., Geyer, C., Pohlmann, B., Klosterkotter, J., 2005. Subjective quality of life in subjects at risk for a first episode of psychosis: a comparison with first episode schizophrenia patients and healthy controls. Schizophr. Res. 79 (1), 137–143.

Beck, A.T., Steer, R.A., 1993. Beck Anxiety Inventory Manual. Harcourt Brace and Company, San Antonio.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56, 893–897.

Beck, A.T., Steer, R.A., Ball, R., Ranieri, W., 1996. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J. Pers. Assess. 67 (3), 588–597.

Cheng, F., Kirkbride, J.B., Lennox, B.R., Perez, J., Masson, K., Lawrence, K., Hill, K., Feeley, L., Painter, M., Murray, G.K., Gallagher, O., Bullmore, E.T., Jones, P.B., 2011. Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting. Psychol. Med. 41 (5), 949–958.

DeVylder, J.E., Oh, A.J., Ben-David, S., Azimov, N., Harkavy-Friedman, J.M., Corcoran, C.M., 2012. Obsessive compulsive symptoms in individuals at clinical risk for psychosis: association with depressive symptoms and suicidal ideation. Schizophr. Res. 140 (1–3), 110–113.

Dhossche, D., Ferdinand, R., Van der Ende, J., Hofstra, M.B., Verhulst, F., 2002. Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. Psychol. Med. 32 (4), 619–627.

Dolle, K., Scheulte-Korne, G., O'Leary, A.M., von Hofacker, N., Izat, Y., Allgaier, A.K., 2012. The Beck Depression inventory-II in adolescent mental health patients: cut-off scores for detecting depression and rating severity. Psychiatry Res. 200 (2–3), 843–848.

Eklund, M., 2009. Work status, daily activities and quality of life among people with severe mental illness. Qual. Life Res. 18, 163–170.

Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33 (6), 766–771.

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2012. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. (Nov 22) Schizophr. Bull. http://dx.doi.org/10.1093/schbul/sbs136.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46 (11), 1006–1011.

Granö, N., Karjalainen, M., Souminen, K., Roine, M., 2011. Poor functioning ability is associated with high risk of developing psychosis in adolescents. Nord. J. Psychiatry 65 (1), 16–21.

Hall, R.C., 1995. Global assessment of functioning. A modified scale. Psychosomatics 36 (3), 267–275.

Hutton, P., Bowe, S., Parker, S., Ford, S., 2011. Prevalence of suicide risk factors in people at ultra-high risk of developing psychosis: a service audit. Early Interv. Psychiatry 5 (4), 375–380.

Jacobson, S., Kelleher, I., Harley, M., Murtagh, A., Clarke, M., Blanchard, M., Connolly, C., O'Hanlon, E., Garavan, H., Cannon, M., 2010. Structural and functional brain correlates of subclinical psychotic symptoms in 11–13 year old schoolchildren. NeuroImage 49 (2), 1875–1885.

Johns, L.C., Cannon, M., Singleton, N., Murray, R.M., Farrell, M., Brugha, T., Bebbington, P., Jenkins, R., Meltzer, H., 2004. Prevalence and correlates of self-reported psychotic symptoms in the British population. Br. J. Psychiatry 185, 298–305.

Jones, P.B., 2013. Adult mental health disorders and their age at onset. Br. J. Psychiatry Suppl. 54, 5–10.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., Molloy, C., Roddy, S., Clarke, M.C., Harley, M., Arseneault, L., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2012a. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. Br. J. Psychiatry (1), 26–32.

Kelleher, I., Lynch, F., Harley, M., Molloy, C., Roddy, S., Fitzpatrick, C., Cannon, M., 2012b. Psychotic symptoms in adolescence index risk for suicidal behavior: findings from 2 population-based case–control clinical interview studies. Arch. Gen. Psychiatry 69 (12), 1277–1283.

© 2013 The Authors. Published by Elsevier B.V. All rights reserved

Kelleher, I., Keeley, H., Corcoran, P., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2013. Childhood trauma and psychosis in a prospective cohort study: cause, effect and directionality. (Apr 19) Am. J. Psychiatry. http://dx.doi.org/10.1176/appi.ajp.2012.

Kendler, K.S., Gallagher, T.J., Abelson, J.M., Kessler, R.C., 1996. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample: the National Comorbidity Survey. Arch. Gen. Psychiatry 53 (11), 1022–1031.

Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R., 2003. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch. Gen. Psychiatry 60 (7), 709–717.

Lataster, T., Collip, D., Lardinois, M., Van Os, J., Myin-Germeys, I., 2010. Evidence for a familial correlation between increased reactivity to stress and positive psychotic symptoms. Acta Psychiatr. Scand. 122, 395–404.

Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean. Schizophr. Res. 79 (2–3), 231–238.

McGorry, P.D., Nelson, B., Phillips, L.J., Yuen, H.P., Francey, S.M., Thampi, A., Berger, G.E., Amminger, G.P., Simmons, M.B., Kelly, D., Thompson, A.D., Yung, A.R., 2012. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. (Nov 27) J. Clin. Psychiatry. http://dx.doi.org/10.4088/JCP.12m07785.

Morrison, A.P., French, P., Stewart, S.L., Birchwood, M., Fowler, D., Gumley, A.I., Jones, P.B., Bentall, R.P., Lewis, S.W., Murray, G.K., Patterson, P., Brunet, K., Conroy, J., Parker, S., Reilly, T., Byrne, R., Davies, L.M., Dunn, G., 2012. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ 344 (5), 2233.

Murray, G.K., Jones, P.B., 2012. Psychotic symptoms in young people without psychotic illness: mechanisms and meaning. Br. J. Psychiatry 201 (1), 4–6.

Palmier-Claus, J.E., Taylor, P.J., Gooding, P., Dunn, G., Lewis, S.W., 2012. Affective variability predicts suicidal ideation in individuals at ultra-high risk of developing psychosis: an experience sampling study. Br. J. Clin. Psychol. 51 (1), 72–83.

Preti, A., Meneghelli, A., Pisano, A., Cocchi, A., Programma 2000 Team, 2009. Risk of suicide and suicidal ideation in psychosis: results from an Italian multi-modal pilot program on early intervention in psychosis. Schizophr. Res. 113 (2–3), 145–150.

Priebe, S., Huxley, P., Knight, S., Evans, S., 1999. Application and results of the Manchester Short Assessment of Quality of Life (MANSA). Int. J. Soc. Psychiatry 45, 7–12.

Salokangas, R.K., Ruhrmann, S., von Reventlow, H.G., Heinimaa, M., Svirskis, T., From, T., Luutonen, S., Juckel, G., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Schultze-Lutter, F., Klosterkötter, J., EPOS group, 2012. Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophr. Res. 138 (2–3), 192–197.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33.

van Os, J., Hanssen, M., Bijl, R.V., Vollebergh, W., 2001. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban–rural comparison. Arch. Gen. Psychiatry 58 (7), 663–668.

van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009. A systematic review and meta-analysis of the continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychol. Med. 39, 179–195.

Velthorst, E., Nieman, D.H., Linszen, D., Becker, H., de Haan, L., 2010. Disability in people clinically at high risk of psychosis. Br. J. Psychiatry 197, 278–284.

Wigman, J.T., van Nierop, M., Vollebergh, W.A., Lieb, R., Beesdo-Baum, K., Wittchen, H.U., van Os, J., 2012. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity—implications for diagnosis and ultra-high risk research. Schizophr. Bull. 38 (2), 247–257.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensibility. Br. J. Psychiatry 133, 429–435.

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust. N. Z. J. Psychiatry 39 (11–12), 964–971.

Yung, A.R., Yuen, H.P., Berger, G., Francey, S., Hung, T.C., Nelson, B., Phillips, L., McGorry, P., 2007. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk. Schizophr. Bull. 33 (3), 673–681.

Zimbrón, J., Ruiz de Azúa, S., Khandaker, G.M., Gandamaneni, P.K., Crane, C.M., González-Pinto, A., Stochl, J., Jones, P.B., Pérez, J., 2012. Clinical and sociodemographic comparison of people at high-risk for psychosis and with first-episode psychosis. Acta Psychiatr. Scand. 127 (3), 210–216.

Appendix 10 Substance use in people at clinical high-risk for psychosis

Russo *et al. BMC Psychiatry* (2014) 14:361
DOI 10.1186/s12888-014-0361-1

BMC Psychiatry

RESEARCH ARTICLE Open Access

Substance use in people at clinical high-risk for psychosis

Debra A Russo[1,2,5*], Jan Stochl[3], Michelle Painter[1], Peter B Jones[1,2,4] and Jesus Perez[1,2]

Abstract

Background: Some high-risk (HR) mental states for psychosis may lack diagnostic specificity and predictive value. Furthermore, psychotic-like experiences found in young populations may act not only as markers for psychosis but also for other non-psychotic psychiatric disorders. A neglected consideration in these populations is the effect of substance misuse and its role in the development of such mental states or its influence in the evolution toward full psychotic presentations. Therefore, the main aim of this study was to thoroughly describe past and current substance use profiles of HR individuals by comparing a consecutive cohort of young people at high risk referred to a population-based early intervention clinical service with a random sample of healthy volunteers (HV) recruited from the same geographical area.

Methods: We compared alcohol and substance use profiles of sixty help-seeking HR individuals and 60 healthy volunteers (HV). In addition to identification of abuse/dependence and influence on psychotic-like experiences, differences between HR individuals and HV were assessed for gender, ethnicity, occupational status, age of lifetime first substance use, prevalence and frequency of substance use.

Results: There were no cases of substance use disorder or dependence in either groups. HR individuals were significantly younger than HV when they first started to use substances ($p = 0.014$). The prevalence of overall HR substance use was similar to that of HV. Although HR individuals reported less cannabinoid use than HV currently (15% vs. 27%), and more in the past (40% vs. 30%), the differences were not statistically significant ($p = 0.177$ & 0.339 respectively). Current frequency of use was significantly higher for HR individuals than HV for alcohol ($p = 0.001$) and cannabinoids ($p = 0.03$). In this sample, only 5% of HR individuals converted to psychosis over a two-year follow-up.

Conclusions: Certain profiles of substance use could potentially play a significant part in the evolution of HR presentations. Therefore, substance use may well represent a clinical domain that requires further emphasis and more detailed consideration in future studies.

Keywords: Alcohol, Cannabis, High-risk, Psychosis, Substance use

Background

It is noteworthy that overall transition rates reported in different cohorts of individuals at clinical high-risk for psychosis (HR) have consistently declined over the last decade [1]. Also, conversion rates have varied across different centers world-wide [1,2]. These discrepancies have been associated with a variety of factors. For example, it has been suggested that the ultimate level of current conversions may not be so low or diverse if high risk individuals were monitored for both longer and comparable follow-up periods [2]. In addition, early detection might indirectly involve provision of non-specific clinical care. Supportive therapy and/or pharmacological interventions, including antidepressants or anxiolytics could reduce stress and subsequently, the likelihood of conversion into frank psychotic disorders. Also, by detecting this group earlier some recent cohorts may have included more false positives than previous studies. In other words, early detection of these mental states may also identify HR phenotypes that could eventually take different diagnostic

* Correspondence: dr335@medschl.cam.ac.uk
[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[2]Department of Psychiatry, University of Cambridge, Cambridge, UK
Full list of author information is available at the end of the article

BioMed Central

© 2014 Russo et al.; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

© 2014 Russo *et al.*; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

trajectories [1,2]. Accordingly, some HR mental states for psychosis may lack diagnostic specificity and predictive value. In fact, presence of psychotic-like symptoms in young people with disorders of anxiety and depression is more prevalent than previously considered [3,4]. Furthermore, psychotic-like experiences found in adolescent populations may act not only as markers for psychosis but also for other non-psychotic psychiatric disorders [5].

Notably, none of these hypotheses have considered the effect of substance misuse in HR individuals and its role in the development of such mental states or its influence in the evolution toward full psychotic presentations. This seems particularly pertinent as alcohol and drug misuse is common among people with psychotic illnesses, including those suffering from a first-episode, and significantly more prevalent than in the general population [6-8]. Moreover, the abuse of illicit substances, such as cannabis, has been positively associated with the development of psychotic disorders [9,10]. A recent literature review suggested that increased rates of substance misuse in HR individuals may be associated with transitions to psychosis. However, it was also highlighted that this evidence was limited by the low number of studies that considered this variable, variety of results and scarce information regarding change of patterns of use over time. Moreover, the vast majority of studies evaluated in this review neither recorded alcohol misuse nor included a comparative group of representative healthy volunteers (HV) in order to better determine possible differences with regard to substance use habits in those individuals at HR [11].

This review also revealed that only diagnostic structured interviews were employed to assess substance use. These tools exclusively focus on the identification of substance abuse and/or dependence [11]. Therefore, it would be preferable to employ a tool to accurately measure alcohol and drug use and enable a complete evaluation of substance use that does not necessarily reach the category of dependence and/or abuse.

Given the paucity of studies primarily addressing the impact of alcohol and drug misuse in HR populations, the main aim of this study was to thoroughly describe past and current substance use profiles of HR individuals by comparing a consecutive cohort of young people at HR referred to a population-based early intervention clinical service with a random sample of HV recruited from the same geographical area.

Methods

Setting

CAMEO (http://www.cameo.nhs.uk) is an early intervention in psychosis service which offers management for people aged 14-35 years suffering from first-episode psychosis in Cambridgeshire, UK. CAMEO also accepts referrals of people at HR. Referrals are accepted from multiple sources including general practitioners, other mental health services, school and college counselors, relatives and self-referrals [12].

Sample

A consecutive cohort of 60 help-seeking individuals, aged 16-35, referred to CAMEO from February 2010 to September 2012 met criteria for HR, according to the Comprehensive Assessment of At Risk Mental States (CAARMS) [13]. In our sample, all individuals fulfilled criteria for the attenuated psychotic symptoms group. Seven individuals (11.7%) also qualified for the vulnerability traits group. The only exclusion criteria were confirmed intellectual disability (Wechsler Adult Intelligence Scale – tested IQ <70), or prior total treatment with antipsychotics for more than one week.

During the same period (February 2010-September 2012), a random sample of 60 HV was recruited by post, using the Postal Address File (PAF®) provided by Royal Mail, UK. To ensure that each HR and HV resided in the same geographical location, 50 corresponding postcodes, matching the first 4/5 characters and digits of each recruited HR individual (e.g. PE13 5; CB5 3), were randomly selected using Microsoft SQL Server, a relational database management system, in conjunction with the PAF database. Each of these 50 addresses was sent a recruitment flyer containing a brief outline of the study, inclusion criteria and contact details. If this failed to generate recruits, a consecutive sample of postcodes was selected. This process was repeated until a match was recruited. HV interested in the study could only participate if they were aged 16-35, resided in the same geographical area as HR individuals (Cambridgeshire), and did not have previous contact with mental health services.

Ethical approval

Ethical approval was granted by the Cambridgeshire East Research Ethics Committee.

Measures

Sociodemographic information (age, gender, ethnicity and occupational status) was collected for all individuals.

HR individuals were interviewed by senior trained psychiatrists working in CAMEO, using the Mini International Neuropsychiatric Interview (MINI), Version 6.0.0 [14], a brief structured diagnostic interview for DSM-IV Axis I psychiatric disorders.

The Positive and Negative Syndrome Scale (PANSS) [15] for psychotic symptoms was also employed to capture the severity of positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items) in a 7-point scale, with higher scores indicating greater severity of illness. These assessments

were carried out by senior research clinicians trained to administer each of the measurement tools.

A novel substance use tool was used to record the specific type of drug and categorised it according to chemical constituents; these comprised sedatives, hallucinogens, dissociatives, cannabinoids, stimulants, opiates, solvents, alcohol and other substances (e.g. legal highs). Frequency was measured using 8 categories: never, one off, less than once a month, once a month, once or twice a week, 3-6 times a week, daily use and uncertain frequency. Quantity measures were excluded as they could lack validity due to the possible inaccuracy in self-reports of drug purity, variety and the size of drug doses. Age at first use was also recorded as age of first substance use has been found to predate initial psychotic symptoms by several years [8,10] and has been associated with the onset of prodromal symptoms [10,16]. It has been suggested that individuals may use substances to self-medicate following the onset of psychotic symptoms [17]. Conversely, it has been argued that substance misuse might cause psychotic symptoms or increase the likelihood of psychotic symptoms in already vulnerable individuals [10,18,19]. Therefore, questions were added to capture a) whether any unusual experiences were experienced under the influence of drugs or alcohol and b) whether drugs or alcohol were used to relieve any unusual symptoms. Individuals were asked about their current drug and alcohol use (now and within the last 3 months) and their greatest past use (period of time prior to the last three months when drug and alcohol use was at its greatest). It was not possible to discern the extent to which individuals deny or exaggerate alcohol and drug use. To minimise this, participants were assessed during a face to face interview which took place over several sessions. This provided confidentiality and enabled the interviewer to build a rapport with the participant, both of which have been shown to increase the validity of self-report [20].

Statistical analysis

Differences between HR individuals and HV were assessed using two sample *t*-test for approximately normally distributed continuous variables (age) and Fisher's exact test for categorical variables (gender, ethnicity and occupational status). Fisher's exact test was also used for assessing the differences between substance use distributions and patterns as this is more appropriate for smaller sample sizes. Wilcoxon signed rank test was employed for non-normally distributed continuous variables (age of lifetime first substance use, frequency of substance use). Boxplots were used for graphical representation of the differences in frequency of substance use.

Results

Sociodemographic profile

Sociodemographic information was collected, comprising age, gender, ethnicity and occupational status. Table 1 shows a comparison between HR and HV individuals. There was a difference in age between the two groups; HV were significantly older than the HR individuals (22.6 SD = 5.7 vs. 19.9 SD = 2.4; p = < 0.001). The HR group had a slightly higher proportion of males and the HV group had a slightly higher proportion of females. Both groups were predominantly white with a similar proportion of Mixed, Asian and Black participants. Both groups contained the same number of students (41.7%), but significantly more HV were employed (p = 0.001).

Psychiatric diagnoses and PANSS scores

We obtained MINI DSM-IV diagnoses for 55 of the 60 HR individuals. Thirty Eight (69.1%) had more than one DSM-IV psychiatric diagnosis, mainly within the affective and anxiety diagnostic spectra. Primary diagnoses for this

Table 1 Sociodemographic comparison between HR and HV individuals

Sociodemographic characteristics	HR (n = 60)	HV (n = 60)	p-values
Age at study entry, years (median, min, max, SD)	19.89 (16.41, 30.21, 2.38)	22.60 (16.18, 35.57, 5.68)	< 0.001*
Gender (n, %)			
Male	31 (51.7%)	26 (43.3%)	0.465~
Female	29 (48.3%)	34 (56.7%)	0.465~
Ethnicity (n, %)†			
White	56 (93.3%)	55 (91.7%)	1.000~
Mixed	2 (3.3%)	2 (3.3%)	1.000~
Asian	1 (1.7%)	2 (3.3%)	1.000~
Black	1(1.7%)	1(1.7%)	1.000~
Occupational status (n, %) (7)‡			
Unemployed	20 (33.3%)	8 (13.%)	0.004~
Employed	8 (13.3%)	27 (45.0%)	0.001~
Students	25 (41.7)	25 (41.7)	0.575~

'P- values' * = *t*-test ~ = Fisher's exact.
† 'White ethnicity' refers to subjects who are White British, White Irish, or other White backgrounds.
'Mixed ethnicity' refers to those who are White and Black Caribbean, mixed White and Black African, mixed White and Asian, or any other mixed backgrounds.
'Asian ethnicity'refers to those who are Indian or Chinese.
'Black ethnicity' refers to subject from any Black backgrounds.
‡ Occupational status is broadly categorized into 3 groups.
'Unemployed' includes subjects who do not have a job, either they are looking for work, not looking for work (e.g., housewife), or not being able to work due to medical reasons.
'Employed'refers to people who have full/part-time employment, or employed but currently unable to work.
'Students' refers to full/part-time students, including those who are also working some hours.

© 2014 Russo *et al.*; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

group were ranked as follows: major depressive episode, current or recurrent (n = 26; 47.3%) > social phobia (n = 7; 12.7%) = generalised anxiety disorder (n = 7; 12.7%) > obsessive compulsive disorder (n = 5; 9.1%) > bipolar disorder, type II (n = 2; 3.6%) > panic disorder (n = 1; 1.8%) = posttraumatic stress disorder (n = 1; 1.8%). Six HR individuals (10.9%) did not fulfill sufficient criteria for a DSM-IV Axis I diagnosis. None of the participants had a substance use disorder. The study protocol did not routinely administer a MINI for HV. However, if the information elicited with the substance use questionnaire indicated that substance use was approaching the threshold for abuse or dependence the protocol was to administer a MINI for verification. This was not the case for any of the HV.

The mean PANSS scores for the HR group comprised positive symptoms (13.1, SD = 3.2), negative symptoms (12.4, SD = 5.0) and general psychopathology (32.7, SD = 7.0). These scores indicated a "mildly ill" group with regards to psychotic symptoms [21]. Psychotic symptoms for the HV group were subclinical: 7.1 (SD = 0.4) for positive symptoms, 7.8 (SD = 0.8) for negative symptoms and 16.4 (SD = 1.3) for general psychopathology.

Substance use

Distribution of substance use

Table 2 shows the number and percentages of individuals who were using each of the substances at the time of their referral to CAMEO. Alcohol and cannabinoids were the most prevalent for both the HR and HV groups.

Table 3 shows how many of the HR and HV individuals were not using any substances, using only one substance (mono-drug) and more than one substance (poly-drug) currently and in the past. Interestingly, more HR individuals (52%) than HV (12%) indicated that they did not use any substance currently (p = 0.001). Although 42% of HR individuals and 32% of HV abstained from using any substance in the past, this difference was not statistically significant (p = 0.343). A significantly higher proportion of HV disclosed that they were currently using one substance (58% vs. 32%, p = 0.006) but not poly substances (30% vs. 17%, p = 0.131). Similarly, more HV individuals reported using only one substance in the past (p = 0.028). However, the percentage of past poly-drug users was higher for HR individuals (38% vs. 28%), although statistical significance was not reached (p = 0.333).

Table 2 Substance use distribution in HV and HR individuals at the time of referral to CAMEO

	HR(n)	%	HV(n)	%	p-value*
Alcohol	18	30.0	31	51.6	0.025
Cannabinoids	9	15.0	16	26.6	0.177
Dissociatives	1	1.6	0	-	1
Hallucinogens	3	5	4	6.6	1
Opiates	1	1.6	0	-	1
Sedatives	1	1.6	0	-	1
Stimulants	6	6	4	6.6	0.743

P- values: * = Fisher's exact.

Age of lifetime first substance use

When considering all substances, the median age of HR individuals was 13 (SD = 2.2) and 15 (SD = 3.7) for HV. Results of a Wilcoxon signed-rank test revealed that HR individuals were significantly younger than HV when they first started to use substances (p = 0.014). When excluding alcohol, the finding was in the same direction (14, SD = 1.58 vs.16, SD = 2.7; p = 0.020). This suggests that for both groups, initial alcohol consumption happened 1-2 years before drug use commenced.

Current prevalence of substance use

Alcohol and cannabinoids were the most prevalent choice of substance for mono-drug and poly-drug users for both groups. Of the 19 HR individuals that reported currently using only one substance 95% used just alcohol and 5% used just cannabinoids. However, 100% of the 13 HV current mono-drug users reported using only alcohol. Table 4 outlines how many of the 10 HR and 18 HV current poly-drug users endorsed the use of each category of substance. Alcohol, cannabinoids and stimulants were the most likely substances of choice for HR poly-drug users; for HV, it was alcohol and cannabinoids. These findings suggest that HR poly-drug users experimented with a wider range of substances than HV poly-drug users.

Past prevalence of substance use

For both HR and HV individuals, there was a wider range of substances used in the past. A higher proportion of HV (40%) reported past mono use of substances when compared with HR mono-drug users (20%, p = 0.028). In addition to alcohol and cannabinoids, HR mono-drug users also experimented with hallucinogens and stimulants and HV mono-drug users with cannabinoids and opiates.

For past poly use of substances, the number of HR individuals reporting use for each substance was higher with the exception of opiates, which was the same. However, none of the differences reached statistical significance (see table 4). There was also an increase in the range of substances for poly-drug use. Hallucinogens, dissociatives and stimulants were additions for HV compared to dissociatives, sedatives and opiates for HR individuals.

When combining mono-drug and poly-drug users, current alcohol use was similar with 47% of HR individuals and 52% of HV endorsing use (p = 0.715). Similarly, there was no significant difference in the amount of alcohol use disclosed by HV (65%) and HR individuals (48%,

Table 3 Substance use pattern in HR and HV individuals

	Current					Past				
	HR(n)	%	HV(n)	%	p value*	HR(n)	%	HV(n)	%	p-value*
No	31	52	7	12	<0.001	25	42	19	32	0.343
Mono-drug	19	32	35	58	0.006	12	20	24	40	0.028
Poly-drug	10	17	18	30	0.131	23	38	17	28	0.333

P- values: * = Fisher's exact.

p = 0.197). For cannabinoids, there were slight differences in current and past use. Fewer HR individuals acknowledged cannabinoid use than HV at the time of their referral to CAMEO (15% vs. 27%), but more HR individuals endorsed use in the past (40% vs. 30%). However, these differences were not statistically significant (p = 0.177 & 0.339 respectively).

Frequency of substance use

Figure (1a) shows the frequency of current use for the most prominent substances. The median frequency of use was significantly higher for HR individuals than HV for alcohol (p = 0.001) and cannabinoids (p = 0.03), but not for hallucinogens (p = 0.386) and stimulants (p = 0.593). Combined with the previous results, this indicates that although the proportion of HV that drank alcohol and use cannabinoids was higher in general, HR individuals used these substances more frequently.

Figure (1b) shows the frequency of past use for the most prominent substances. There were no significant differences in past frequency of use for any of the substances with the exception of hallucinogens. HV used hallucinogens significantly more often than HR individuals (p = 0.037). This suggests that frequency of substance use for HR individuals remained similar for current and past use; whereas HV were more likely to have a period in the past where they used hallucinogens more frequently.

Experience or relief of psychotic-like experiences

Eleven percent of HR individuals reported experiencing psychotic-like symptoms under the influence of substances and 10% reported using substances to help relieve these experiences. All the HV denied psychotic-like experiences under the influence of substances or using substances to help relieve these symptoms.

Discussion

The main aim of this study was to thoroughly describe past and current substance use profiles of HR individuals and compare them with a sample of healthy volunteers. Results showed that, for overall substance use, the prevalence of HR substance use was less or similar to that of HV. The ony exception to this was past poly-drug use, which was sightly higher for HR individuals, although not statistically significant. HR poly-drug users experimented with a wider range of substances than HV poly-drug users. HR individuals were significantly younger than HV when they started using alcohol and drugs. Choice of substance was similar when comparing HR and HV individuals' current and past use. Alcohol was the most frequently reported substance used in both groups. In terms of illicit substances, cannabis was the most widely used drug in both groups. The use of other illicit substances was considerably lower compared with cannabis. The least used substances for both groups were sedatives and opiates.

Table 4 Number of HR and HV individuals that endorsed using each substance for current and past mono-drug and poly-drug use

	Current						Past					
	Mono-drug Users			Poly-drug Users			Mono-drug Users			Poly-drug Users		
	HR (n=19)	HV (n=35)	p-value*	HR (n=10)	HV (n=18)	p-value*	HR (n=12)	HV (n=24)	p-value*	HR (n=23)	HV (n=17)	p-value*
Alcohol	18	13	0.404	10	18	0.130	8	21	0.010	22	17	0.436
Cannabinoids	1	0	1	8	16	0.109	2	2	1	22	16	0.327
Dissociatives	0	0	1	1	0	1	0	0	1	6	2	0.272
Hallucinogens	0	0	1	3	4	1	1	1	1	6	4	0.743
Opiates	0	0	1	1	0	1	0	1	1	3	3	1
Sedatives	0	0	1	1	0	1	0	0	1	1	0	1
Stimulants	0	0	1	6	4	0.743	1	0	1	15	9	0.254

P- values: * = Fisher's exact.

© 2014 Russo *et al.*; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

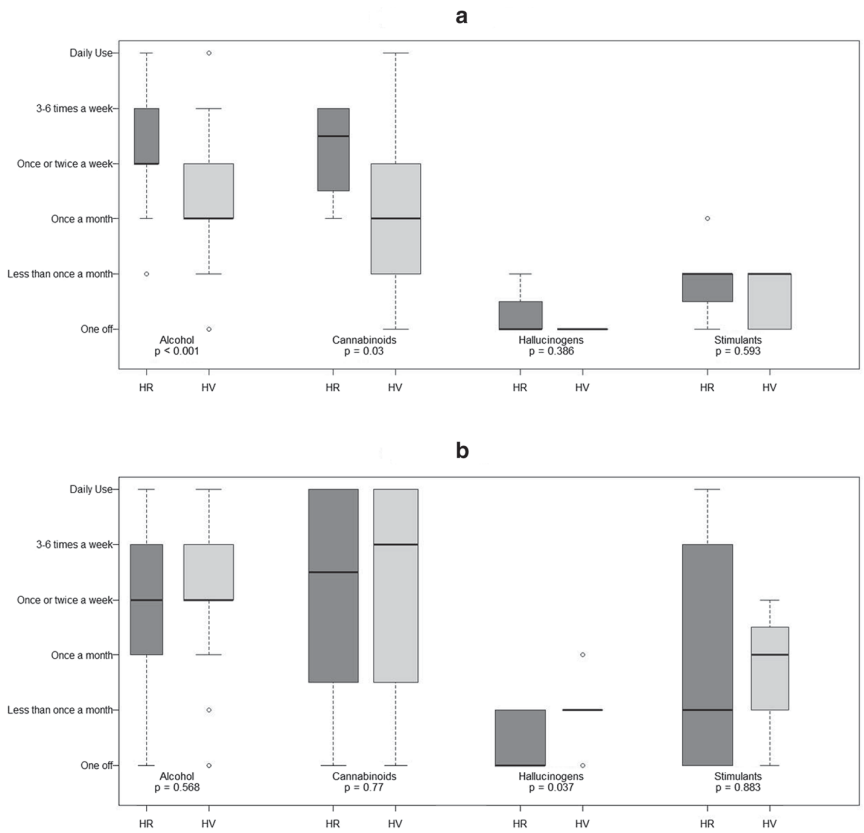


Figure 1 Frequency of substance use in HR and HV individuals. (a) Current frequency of substance use **(b)** Past frequency of substance use.

Addington et al.'s recent review of HR individuals revealed that cannabis was the most commonly used substance [11], whereas in the present study it was alcohol. Rates of use varied from 33% to 54%; this was considerably higher than the 9% reporting cannabis use in the present study. However, the prevalence of alcohol use (46.5%) was greater than the highest reported rate in other studies (17% - 44%).

Interestingly, none of the HR or HV individuals included in this study could be categorised as suffering from DSM-IV substance use disorder or dependence. This is not only significantly different to the severity of use reported in other HR samples [11], but also to a population-based sample of individuals experiencing first-episode psychosis from the same early intervention service [8]. In this cross sectional analysis cannabis abuse or dependence and alcohol abuse or dependence was reported in approximately 50% of CAMEO first episode psychosis (FEP) patients. In addition, 38% disclosed poly substance abuse and more than half of them used Class A drugs. These findings were also replicated in FEP samples from other countries [22].

Therefore, the HR substance use profile in the present sample was not only different to HV from the same geographical area, it also appears to differ from first-episode psychosis patients in our region at the time of their referral to CAMEO. This is further substantiated by the fact that after approximately 2 years of an antipsychotic-free follow-up period for each individual at HR in this sample, only 3 (5%) made a transition to a psychotic disorder. One possible conclusion to be drawn is that their pattern of use could have some influence on psychotic-like experiences but not on transition to a frank psychotic disorder. Nevertheless, the frequent diagnosis of mood or anxiety disorders in this sample supplicates the consideration that substance use may also have had an impact these outcomes. However, the cross-sectional design of our study did not allow the consideration of the role substance use in the evolution of other non-psychotic psychiatric disorders.

The main difference between HR individuals and HV was frequency of substance use. Current frequency of use was significantly higher in HR individuals than HV for alcohol and cannabinoids. However, daily use of cannabis in

our HR group (0%) was much lower than in other studies, which found this frequency in around 60% of their HR samples [23,24]. Cannabis use once to twice a week occurred in 7% of our HR individuals in comparison to 20% [23] and 19% [24] in previous studies. The one study that reported frequency of alcohol use found similar drinking behaviours in HR and HV individuals [25].

Notably, the frequency of substance use for HR individuals, particularly for alcohol and cannabinoids, remained similar for current and past use; whereas HV were more likely to have a period in the past where they used these substances more frequently. This could suggest that sustained substance use over a protracted period could be more deleterious than a shorter period of increased use. Furthermore, the higher frequency of substance use in HR individuals combined with a significantly younger age of first use might eventually contribute to the development of psychotic-like experiences.

The hypothesis that some individuals may use substances to alleviate psychotic symptoms [17] was not supported in this study. In fact, very few HR individuals reported using substances to help relieve these experiences.

The results of this study must be considered in the light of the following limitations. The multiple incidences of depression and anxiety combined with the lack of transitions may call in to question the authenticity of our HR sample. However, co-morbidity of disorders of anxiety and depression with psychotic symptoms appears to be more prevalent than previously considered in adolescents and young adults [3]. Added to this, the short follow-up in this study could explain the low transition rate. Transitions can occur up to 10 years after psychotic symptoms first emerge [26]. Moreover, the 3 monthly follow-ups in this study may have been therapeutic, indirectly providing non-specific clinical care and consequently reducing the likelihood of transition. Certainly, scrutiny of the follow-up intervals in Addington's review [11] revealed diverse monitoring periods, in addition to varied transition rates. Therefore, drawing valid conclusions on this issue is complex. Also, the pattern of substance use was not closely monitored for each individual after the time of their referral to CAMEO. Future research should address this limitation since prospective follow-up could reveal changes in patterns of substance use that could have an impact on the incidence of psychotic experiences over time. The small sample size of 60 participants is acknowledged. However, this number is greater or comparable to over half the studies in Addington's review [11].

The sociodemographic differences in our sample compared to other HR samples in the literature are also potential limitations. Firstly, HV were significantly older than HR individuals. However, the influence of this dissimilarity in the domains that were significantly different between both groups, i.e. age of first substance use and frequency of substance use, was arguably negligible. Secondly, there is a geographical difference compared to other research describing substance use in HR samples. Although the majority of studies in Addington's review [11] were conducted in USA and Australia, several were conducted in Europe. However, none were exclusively in the UK. Despite the limitations of comparing such a diverse geographical spread of HR samples, describing substance use in a UK sample of HR individuals provides a useful contribution to the literature. Thirdly, although there was some representation of different ethnicities, the sample was predominantly white. Comparisons with the existing literature on substance use in HR samples are problematic as the majority of studies did not report ethnicity or they dichotomised the categories e.g. white vs non-white (see Addington et al. [11]). Finally, while the gender ratio did not differ significantly between HR and HV groups, the slightly higher proportion of males in the HR group may have influenced the patterns of substance use, as male gender is associated with substance use in patients and psychotic disorders in the general population [27].

Conclusions

Research on individuals at HR is showing a remarkable variability in clinical outcomes across different samples worldwide. This is further corroborated by the difference between the characteristics of the current HR sample and other studies in this field. Although this is probably due to a variety of factors, including both biological and psychological components, certain profiles of substance use could potentially play a significant part in the evolution of these presentations. Therefore, substance use may well represent a clinical domain that requires further emphasis and more detailed consideration in future studies.

Abbreviations

CAARMS: Comprehensive assessment of at-risk-mental-states; HR: Clinical high-risk for psychosis; HV: Healthy volunteers; MINI: Mini international neuropsychiatric interview; PANSS: The positive and negative syndrome scale.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PBJ is the chief investigator for this study. JP and MP are principal investigator and project manager, respectively. All authors participated in the conception and design of the study. JS performed the statistical analysis, contributed to the interpretation of the data and designed data presentation. JP and DAR drafted the manuscript. All authors provided a critical review and final approval of the manuscript.

Acknowledgements

The authors thank the PAATh Study team (Gillian Shelley, Chris McAlinden, Carolyn Crane and Gerhard Smith) and all members of CAMEO services for their help and support in the elaboration of this study.
This work was supported by the National Institute for Health Research (NIHR; programme grant RP-PG-0606-1335 'Understanding Causes and Developing

© 2014 Russo *et al.*; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Effective Interventions for Schizophrenia and Other Psychoses' awarded to P. B.J.). The work forms part of the NIHR Collaboration for Leadership in Applied Health Research & Care for Cambridgeshire & Peterborough (CLAHRC-CP). The NIHR had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Author details
[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK. [2]Department of Psychiatry, University of Cambridge, Cambridge, UK. [3]Department of Health Sciences, University of York, York, UK. [4]NIHR Collaboration for Leadership in Applied Health Research & Care, Cambridge, UK. [5]Block 7, Ida Darwin Site, Fulbourn Hospital, CB21 5EE Fulbourn, Cambridge, UK.

Received: 27 March 2014 Accepted: 11 December 2014
Published online: 24 December 2014

References

1. Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, Phillips L, McGorry P: **Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk?** *Schizophr Bull* 2007, **33:**673–681.
2. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P: **Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk.** *Arch Gen Psychiatry* 2012, **69:**220–229.
3. Wigman JT, van Nierop M, Vollebergh WA, Lieb R, Beesdo-Baum K, Wittchen HU, van Os J: **Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity - implications for diagnosis and ultra-high risk research.** *Schizophr Bull* 2012, **38:**247–257.
4. Hui C, Morcillo C, Russo DA, Stochl J, Shelley GF, Painter M, Jones PB, Perez J: **Psychiatric morbidity and disability in young people at clinical high risk for psychosis.** *Schizophr Res* 2013, **148:**175–180.
5. Kelleher I, Keeley H, Corcoran P, Lynch F, Fitzpatrick C, Devlin N, Molloy C, Roddy S, Clarke MC, Harley M, Arseneault L, Wasserman C, Carli V, Sarchiapone M, Hoven C, Wasserman D, Cannon M: **Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies.** *Br J Psychiatry* 2012, **1:**26–32.
6. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK: **Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study.** *JAMA* 1990, **21:**2511–2518.
7. McCreadie RG: **Scottish Comorbidity Study Group: Use of drugs, alcohol and tobacco by people with schizophrenia: case – control study.** *Br J Psychiatry* 2002, **181:**321–325.
8. Barnett JH, Werners U, Secher SM, Hill KE, Brazil R, Masson K, Pernet DE, Kirkbride JB, Murray GK, Bullmore ET, Jones PB: **Substance use in a population-based clinic sample of people with first-episode psychosis.** *Br J Psychiatry* 2007, **190:**515–520.
9. Fergusson DM, Poulton R, Smith PF, Boden JM: **Cannabis and psychosis.** *BMJ* 2006, **21:**172–175.
10. Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, Dingemans PM, Birchwood M, Patterson P, Salokangas RK, Heinimaa M, Heinz A, Juckel G, Graf von Reventlow H, French P, Stevens H, Ruhrmann S, Klosterkötter J, Linszen DH, EPOS group: **Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis.** *Acta Psychiatr Scand* 2012, **125**(1):45–53.
11. Addington J, Case N, Saleem MM, Auther AM, Cornblatt BA, Cadenhead KS: **Substance use in clinical high risk for psychosis: a review of the literature.** *Early Interv Psychiatry* 2013, doi:10.1111/eip.12100 [Epub ahead of print].
12. Cheng F, Kirkbride JB, Lennox BR, Perez J, Masson K, Lawrence K, Hill K, Feeley L, Painter M, Murray GK, Gallagher O, Bullmore ET, Jones PB: **Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting.** *Psychol Med* 2011, **41:**949–958.
13. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J: **Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States.** *Aust N Z J Psychiatry* 2005, **39:**964–971.
14. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: **The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.** *J Clin Psychiatry* 1998, **59:**22–33.
15. Kay SR, Fiszbein A, Opler LA: **The positive and negative syndrome scale (PANSS) for schizophrenia.** *Schizophr Bull* 1987, **13:**261–276.
16. Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, Esterberg ML, Stewart T, Walker EF: **Relations of Pre-Onset Cannabis, Alcohol, and Tobacco Use with the Age at Onset of Prodrome and Age at Onset of Psychosis in First-Episode Patients.** *Am J Psychiatry* 2009, **166:**1251–1257.
17. Phillips P, Johnson S: **How does drug and alcohol misuse develop among people with psychotic illnesses? A literature review.** *Soc Psychiatry Psychiatr Epidemiol* 2001, **36:**269–276.
18. Hall W, Degenhardt L: **Cannabis use and the risk of developing a psychotic disorder.** *World Psychiatr* 2008, **7:**68–71.
19. Kamali M, McTigue O, Whitty P, Gervin M, Clarke M, Browne S, Larkin C, O'Callaghan E: **Lifetime history of substance misuse in first episode psychosis: prevalence and its influence on psychopathology and onset of psychotic symptoms.** *Early Interv Psychiatry* 2009, **3:**198–203.
20. Winters KC: *Assessing Alcohol Problems - A Guide for Clinicians and Researchers* Second Edition NIH Publication No. 03–3745 Revised 2003 [http://pubs.niaaa.nih.gov/publications/assessingalcohol/index.htm]
21. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR: **What does the PANSS mean?** *Schizophr Res* 2005, **79:**231–238.
22. Addington J, Addington D: **Patterns, predictors and impact of substance use in early psychosis: a longitudinal study.** *Acta Psychiatr Scand* 2007, **115:**304–309.
23. Dragt S, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, de Haan L, van Amelsvoort TA, Linszen DH: **Age of onset of cannabis use is associated with age of onset of high-risk symptoms for psychosis.** *Can J Psychiatry* 2010, **55:**165–171.
24. Korver N, Nieman DH, Becker HE, van de Fliert JR, Dingemans PH, de Haan L, Spiering M, Schmitz N, Linszen DH: **Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls.** *Aust N Z J Psychiatry* 2010, **44:**230–236.
25. Auther AM, McLaughlin D, Carrión RE, Nagachandran P, Correll CU, Cornblatt BA: **Prospective study of cannabis use in adolescents at clinical high risk for psychosis: impact on conversion to psychosis and functional outcome.** *Psychol Med* 2012, **42:**2485–2497.
26. Nelson B, Yuen H, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, Broussard C, Simmons M, Foley DL, Brewerm WJ, Francey SM, Amminger GP, Thompson A, McGorry PD, Yung AR: **Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study.** *JAMA Psychiatr* 2013, **70**(8):793–802.
27. Barkus E, Murray RM: **Substance use in adolescence and psychosis: Clarifying the relationship.** *Annu Rev Clin Psychol* 2010, **6:**365–389.

Submit your next manuscript to BioMed Central and take full advantage of:

- **Convenient online submission**
- **Thorough peer review**
- **No space constraints or color figure charges**
- **Immediate publication on acceptance**
- **Inclusion in PubMed, CAS, Scopus and Google Scholar**
- **Research which is freely available for redistribution**

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

Appendix 11 Trauma history characteristics associated with mental states at clinical high risk for psychosis

Psychiatry Research 220 (2014) 237–244

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Trauma history characteristics associated with mental states at clinical high risk for psychosis

Debra A. Russo [a,b], Jan Stochl [a,b], Michelle Painter [a], Veronika Dobler [b], Erica Jackson [a], Peter B. Jones [a,b,c], Jesus Perez [a,b,*]

[a] CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, UK
[b] Department of Psychiatry, University of Cambridge, Cambridge, UK
[c] NIHR Collaboration for Leadership in Applied Health Research & Care, Cambridge, UK

ARTICLE INFO

Article history:
Received 9 July 2013
Received in revised form
14 August 2014
Accepted 17 August 2014
Available online 27 August 2014

Keywords:
At-risk-mental-state
High-risk
Psychotic-like
Schizophrenia
Trauma

ABSTRACT

Traumatic experiences have been positively associated with both severity of attenuated psychotic symptoms in individuals at high risk (HR) for psychosis and transitions into psychotic disorders. Our aim was to determine what characteristics of the trauma history are more likely to be associated with individuals at HR. The Trauma History Screen (THS) was used to enable emphasis on number and perceived intensity of adverse life events and age at trauma exposure. Sixty help-seeking individuals who met HR criteria were compared to a random sample of 60 healthy volunteers. Both groups were aged 16–35 and resided in the same geographical location. HR participants experienced their first trauma at an earlier age, continued to experience trauma at younger developmental stages, especially during early/mid adolescence and were exposed to a high number of traumas. They were more depressed and anxious, but did not experience more distress in relation to trauma. Both incidences of trauma and age at which trauma occurred were the most likely predictors of becoming HR. This work emphasises the importance of assessing trauma characteristics in HR individuals to enable differentiation between psychotic-like experiences that may reflect dissociative responses to trauma and genuine prodromal psychotic presentations.
© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Psychosis has been linked with a history of adverse life events (Read et al., 2005; Morgan et al., 2007; Bendall et al., 2008; Bebbington et al., 2011; Fisher et al., 2010; Varese et al., 2012). Traumatic experiences, especially in childhood and early adolescence, appear to be related to psychosis in a dose–response fashion. The number of traumas has been positively associated with severity of attenuated psychotic symptoms in individuals at clinical high risk (HR) for psychosis and, eventually, transitions into frank psychotic disorders (Thompson et al., 2009; Bechdolf et al., 2010)

It is noteworthy that overall transition rates reported in different cohorts of individuals at clinical HR have consistently declined over the last decade (Yung et al., 2007). Subsequently, it has been suggested that HR mental states for psychosis may lack diagnostic specificity and predictive value. Indeed, the presence of psychotic-like symptoms in young people with disorders of anxiety and depression is more prevalent than previously considered (Wigman et al., 2012a; Hui et al., 2013). Furthermore, psychotic-like experiences found in adolescent populations may act not only as markers for psychosis but also for other non-psychotic psychiatric disorders, such as depression and anxiety (Kelleher et al., 2012).

These findings raise the question about whether life stressors should exclusively be investigated as predictors of conversion to psychosis or also as potential contributing factors to HR mental states. In fact, early traumatic life events are common in people at HR (Tikka et al., 2013; Addington et al., 2013) who usually also present with significant morbidity and functional impairment regardless of whether they develop a full-blown psychotic disorder (Zimbron et al., 2012; Hui et al., 2013). Accordingly, addressing trauma in this population might help develop successful therapeutic interventions.

To achieve this ultimate goal it is important to obtain meaningful clinical information that should ideally consider the potential variability in both objective consequences and subjective perceptions after similar traumatic events among different individuals. This element has been neglected in the majority of measures assessing traumatic experiences, which usually survey a broad range of potential stressors and only ask for details of any events endorsed, including those that may not have been significantly distressing (Norris and Hamblen, 2004).

* Corresponding author at: CAMEO Early Intervention Services, Block 7, Ida Darwin Site, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EE, UK. Tel.: +44 1223884360; fax: +44 1223884362.
E-mail address: jp440@cam.ac.uk (J. Perez).

http://dx.doi.org/10.1016/j.psychres.2014.08.028
0165-1781/© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

The importance of assessing the degree to which the objective event was subjectively traumatic has been proposed by Spauwen et al. (2006) and Kelleher et al. (2013) with the inference that this may have an impact on risk for psychotic experiences (Kelleher et al., 2013). In concurrence, Wigman et al. (2012b) recommended using social stress as a proxy measure of sensitisation to traumatic experiences to aid understanding of any interactions between trauma and proneness towards psychosis. Furthermore, Addington et al. (2013) emphasised the need to detail both the age at which the trauma occurred and the frequency of trauma over time. Therefore, different combinations of trauma factors, such as perceived severity and frequency of sudden adverse life events, as well as age at trauma exposure, could help better understand different responses among individuals and the likelihood of developing a particular psychiatric manifestation (Carlson et al., 2011).

Another recognised limitation is the absence of matched healthy controls in studies investigating the relationship between trauma and psychotic symptoms (Thompson et al., 2009). This omission may also affect the conclusions to be drawn with regards to trauma prevalence.

By addressing the limitations of previous research, the aim of this study was to determine what characteristics of the trauma history are more likely to be associated with HR mental states in young people referred to mental health services in comparison with a sample of healthy volunteers recruited from the same geographical area. We particularly focused on the number and perceived intensity of adverse life events and age at trauma exposure.

2. Methods

2.1. Setting

CAMEO (http://www.cameo.nhs.uk) is an early intervention in psychosis service which offers management for people aged 14–35 years suffering from first-episode psychosis (FEP) in Cambridgeshire, UK. CAMEO also accepts referrals of people at HR. Referrals are accepted from multiple sources including general practitioners, other mental health services, school and college counsellors, relatives and self-referrals (Cheng et al., 2011).

2.2. Sample

A consecutive cohort of 60 help-seeking individuals, aged 16–35, referred to CAMEO from February 2010 to September 2012 met criteria for HR, according to the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 2005). Referrals came to our offices via a number of different routes including self-referral, carers and relatives, schools and colleges, but mainly Primary Care. All individuals identified as HR for psychosis living and detected in Cambridgeshire and Peterborough were offered a systematic follow-up in the context of a prospective, naturalistic study called PAATH: Prospective Analysis of At-risk-mental-states and Transitions into PsycHosis. Participants were followed-up for 2 years from the initial referral date. During this period, they were asked to attend subsequent interviews where they completed structured interviews and questionnaires. These questionnaires targeted different domains, such as socio-demographic characteristics, diagnosis, psychiatric morbidity, trauma history, substance use and functioning, among others.

In our sample, all individuals fulfilled criteria for the attenuated psychotic symptoms group. Seven individuals (11.7%) also qualified for the vulnerability traits group (individuals with a family history of psychosis in first degree relative OR schizotypal personality disorder PLUS a 30% drop in GAF score from premorbid level, sustained for a month, occurred within the past 12 months OR GAF score of 50% or less for the past 12 months). Intake exclusion criteria included: i) acute intoxication or withdrawal associated with drug or alcohol abuse or any delirium, ii) confirmed intellectual disability (Wechsler Adult Intelligence Scale – tested IQ < 70), or iii) prior total treatment with antipsychotics for more than 1 week.

During the same period (February 2010–September 2012), a random sample of 60 healthy volunteers (HVs) was recruited by post, using the Postal Address File (PAF®) provided by Royal Mail, UK. To ensure that each HR and HV resided in the same geographical location, 50 corresponding postcodes, matching the first 4/5 characters and digits of each recruited HR participant (e.g. PE13 5; CB5 3), were randomly selected using Microsoft SQL Server, a relational database management system, in conjunction with the PAF database. Each of these 50 addresses was sent a recruitment flyer containing a brief outline of the study, inclusion criteria and contact details. If this failed to generate recruits, a consecutive sample of postcodes would be selected. This process was repeated until a match was recruited. An average of 100 flyers was sent to each postcode to recruit the 60 HV participants. HVs interested in the study could only participate if they were aged 16–35, resided in the same geographical area as HR participants (Cambridgeshire), and did not have previous contact with mental health services.

2.3. Ethical approval

Ethical approval was granted by the Cambridgeshire East Research Ethics Committee.

2.4. Measures

All participants were assessed with sociodemographic (age, gender, ethnicity and occupational status), trauma and clinical measures at the time of their referral to CAMEO. The assessments were carried out by senior research clinicians trained in each of the measurement tools.

HR participants were interviewed by senior trained psychiatrists working in CAMEO, using the Mini International Neuropsychiatric Interview (MINI), Version 6.0.0 (Sheehan et al., 1998), a brief structured diagnostic interview for DSM-IV Axis I psychiatric disorders. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) for psychotic symptoms was also employed to capture the severity of positive symptoms (seven items), negative symptoms (seven items) and general psychopathology (16 items) in a 7-point scale, with higher scores indicating greater severity of illness.

To address the limitations of previous trauma measurement tools, the Trauma History Screen (THS; Carlson et al., 2011) was selected for this study. The THS was developed as a brief, easy to complete self-report measure of exposure to both high magnitude stressor events that could be traumatic (HMS) and events associated with significant and persisting posttraumatic distress (PPD). It assesses exposure to severe stressors which the authors define as sudden events that have been found to cause extreme distress in most of those exposed (HMS) and events associated with significant subjective distress that lasts more than a month (PPD) events. The authors propose that the theoretical rational for including the specific stressor categories was that suddenness, lack of controllability, and a strong negative valence are all necessary, although not sufficient, characteristics for an event to cause traumatic stress (Carlson and Dalenberg, 2000).

The THS was developed to provide information about exposure to stressor events and about the severity and duration of emotional responses to stressful events. The reliability and validity of the THS have been demonstrated in clinical and non-clinical samples of homeless veterans, hospital trauma patients and their families, university students and adults and young adults from a community sample (Carlson et al., 2011). The reliability in these samples was good to excellent with median kappa coefficients of agreement for items ranging from 0.61 to 0.77. Construct validity was also supported by findings of strong convergent validity with a longer measure of trauma exposure and by correlations of THS scores between $r = 0.73$ and 0.77 with PTSD symptoms.

This brief measure with a simple format and an easy reading level includes a gate question after the initial trauma checklist which is designed to only record details concerning events that were significantly distressing. The THS assesses trauma load, frequency and the distress caused by the traumatic events. It is a 13-item self-report measure that examines 11 events and one general event, including military trauma, sexual assault and natural disasters. For each event, respondents are asked to indicate whether the event occurred ('yes' or 'no') and the number of times something like this happened. For each event endorsed as emotionally troubling additional dimensions are assessed, including age when it happened, a description of what happened, whether there was actual or a threat of death or injury, feelings of helplessness and feelings of dissociation, a 4-point scale for duration of distress ('not at all' to 'a month or more') and a 5-point scale for distress level ('not at all' to 'very much').

The Beck Depression Inventory, Version II (BDI-II; Beck et al., 1996) and the Beck Anxiety Inventory (BAI; Beck and Steer, 1993) were used to assess depressive and anxiety symptoms respectively. BDI-II and BAI are widely used self-report instruments to assess depressive and anxiety symptom severity in the past 2 weeks. Each of them consists of 21 items rated on a 4-point scale from absent (0), mild (1), moderate (2) to severe (3). Composite scores (range 0–63 points) were generated by summing up individual items. Scores obtained from both measures were then used to analyse possible correlations with age at trauma exposure, number and intensity of traumatic events and associated distress.

2.5. Statistical analysis

All statistical analyses were performed using R software (R Core Team, 2013). For demographic comparisons between HR individuals and healthy volunteers Fisher's exact test was used. Overall number of traumas and age trauma occurred were compared using negative binomial regression. Poisson regression was used to compare individual traumas in both groups. *t*-Test was used for intensity of trauma comparisons. We calculated Pearson correlations to evaluate possible associations

between age at which trauma occurred, number and intensity of traumas, BDI-II and BAI. Logistic regression was used to evaluate the importance of age at trauma exposure, intensity and number of traumas with regards to the presence of HR mental states. We also presented graphical comparisons of both groups using box plots.

3. Results

3.1. Sociodemographic profile

Sociodemographic information was collected, comprising age, gender, ethnicity and occupational status. Table 1 shows a comparison between HR and HV individuals. There was a difference in age between the two groups; HVs were significantly older than the HR participants ($t=-3.97$, d.f.$=86$, $p \leq 0.001$). The HR group had a slightly higher proportion of males and the HV group had a slightly higher proportion of females. Both groups were predominantly white with a similar proportion of Mixed, Asian and Black participants. Both groups contained the same number of students (41.7%), but significantly more HV participants were employed ($p=0.001$).

3.2. Psychiatric diagnoses and PANSS scores

We obtained MINI DSM-IV diagnoses for 55 of the 60 HR individuals. Thirty eight (69.1%) had more than one DSM-IV psychiatric diagnosis, mainly within the affective and anxiety diagnostic spectra. Primary diagnoses for this group were ranked as follows: major depressive episode, current or recurrent ($n=26$; 47.3%) > social phobia ($n=7$; 12.7%)=generalised anxiety disorder ($n=7$; 12.7%) > obsessive compulsive disorder ($n=5$; 9.1%) > bipolar disorder, type II ($n=2$; 3.6%) > panic disorder ($n=1$; 1.8%)= posttraumatic stress disorder ($n=1$; 1.8%). Six HR individuals (10.9%) did not fulfill sufficient criteria for a DSM-IV Axis I diagnosis.

The mean PANSS scores for the HR group comprised positive symptoms (13.1, S.D.$=3.2$), negative symptoms (12.4, S.D.$=5.0$) and general psychopathology (32.7, S.D.$=7.0$). These scores indicated a 'mildly ill' group with regards to psychotic symptoms (Leucht et al., 2005). Psychotic symptoms for the HV group were subclinical. The study protocol did not routinely administer a MINI for HV. However, if information elicited with the battery of questionnaires indicated any concerns about mental state, the protocol was to administer a MINI for verification. This was not the case for any of the HV.

3.3. Trauma history

3.3.1. Number of traumatic events

The THS assesses lifetime exposure to 14 potentially traumatic events. Table 2 shows how many HR and HV participants had experienced an event described on the screen and compares the total number of times each trauma occurred for HR and HV participants. Seventy-five per cent of HR participants reported experiencing at least one trauma in their lifetime, compared to 68% of the HV group. Neither group had experienced a traumatic event during military service. With the exception of a disaster (hurricane, flood, earthquake, tornado, fire) and sudden death of close family or friend, more HR participants had experienced the different types of trauma than HV participants. This finding was replicated in the total number of times each trauma occurred. The mean number of all traumatic events was calculated for HR (8.6, S.D.$=11.4$) and HV (3.2, S.D.$=4.8$) participants (see Fig. 1). Based on a negative binomial model, this difference was statistically significant ($p \leq 0.001$). There was one outlier scoring 69 traumatic events. However, analysis omitting this value revealed no significant differences in the results.

When each type of traumatic event was considered separately, being hit or kicked hard enough to injure, both as a child and an adult, showed the largest differences between HR and HV participants. Further analysis using Poisson regression revealed that physical abuse both as a child ($p \leq 0.001$) and an adult ($p \leq 0.001$), witnessing death or injury ($p \leq 0.001$), events that induced feelings of fear, helplessness or horror ($p \leq 0.001$) and abandonment ($p \leq 0.001$) where significantly more frequent for HR participants than HV participants (see Table 2).

The THS (Carlson et al., 2011) then asks 'Did any of these things really bother you emotionally? NO YES'. The subsequent analyses were conducted only on those events acknowledged as YES. For HR participants, this was 39% of the total number of all traumatic events reported and for HV participants, it was 32.2%.

3.3.2. Intensity of traumatic events

Up to 70% of traumatic events were reported as distressing. To assess the intensity of traumatic events, the mean perceived level of distress for each emotionally troubling event was calculated (How much did it bother you emotionally? not at all/a little/somewhat/much/very much). Fig. 1 shows that experiences of distress were very similar between the groups (HR$=3.1$, S.D.$=1.14$; HV$=3.0$, S.D.$=1.3$). Results of a two sample t-test revealed that there was no significant difference between groups in terms of trauma intensity ($t=0.4175$, d.f.$=84$, $p=0.6774$).

3.3.3. Age traumatic events occurred

Fig. 1 shows that the mean age of exposure to all traumas for HR participants was 13.6 (S.D.$=4.3$, median$=14$) and 17.8 (S.D.$=5.1$, median$=17$) for HV participants. In instances where individuals had more than one exposure to trauma, the mean age was calculated initially. Results of a two sample t-test revealed that HR participants were exposed to trauma at a significantly younger age than HV participants ($t=-3.974$, d.f.$=84$, p-value $<$ 0.001). Further analyses confirmed that the mean age HR participants experienced their first trauma was 9.8 (S.D.$=5.5$, median$=9$), while for HV participants it was 16.5 (S.D.$=6.0$, median$=16$). To determine any prevalent developmental stage that trauma occurred, the number of traumatic events was stratified by age and group. Analyses revealed that, for both groups, the most traumas occurred between the ages of 9–16 and 17–24, with HR volunteers experiencing more trauma than HV participants during both these stages. HR participants experienced significantly more traumas between the ages of 0 and 8 ($p \leq 0.001$). Conversely, HV participants experienced more traumas between the ages of 25 and 35. However, due to the lack of variance within the HR group, significance could not be tested.

3.3.4. Relationship between number of traumas, trauma intensity, age at trauma exposure, depression and anxiety

Cronbach's alphas for the 21 BDI and 21 BAI items were 0.96 and 0.95 respectively, indicating high reliability for both measures.

HR participants had a higher total BDI-II score (i.e., more depressed) than HVs (29.9, S.D.$=12.8$ vs. 6.7, S.D.$=6.5$, $p \leq 0.001$). Similarly, total BAI scores revealed that HR individuals had more anxiety symptoms (28.9, S.D.$=11.9$ vs. 8.5 S.D.$=8.0$, $p \leq 0.001$). Furthermore, 61.7% of HR participants suffered moderate or severe depression and 85.4% suffered moderate or severe anxiety.

Pearson correlation coefficients were calculated for the relationships between among trauma incidence, trauma intensity, depression, anxiety and age (Table 3). Results showed that both BDI and BAI sum scores were significantly correlated with the number of traumatic events and age of trauma. The higher the number of traumatic events, the higher the BDI and BAI scores. Conversely, the lower the age that traumatic events occurred, the

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Table 1
Sociodemographic comparison between HR and HV participants.

Sociodemographic characteristics	HR ($n=60$)	HV ($n=60$)	p-Values
Age at study entry, years (median, min, max, S.D.)	19.89 (16.41, 30.21, 2.38)	22.60 (16.18, 35.57, 5.68)	<0.001*
Gender (n, %)			
Male	31 (51.7%)	26 (43.3%)	0.465~
Female	29 (48.3%)	34 (56.7%)	0.465~
Ethnicity (n, %)†			
White	56 (93.3%)	55 (91.7%)	1.000~
Mixed	2 (3.3%)	2 (3.3%)	1.000~
Asian	1 (1.7%)	2 (3.3%)	1.000~
Black	1(1.7%)	1(1.7%)	1.000~
Occupational status (n, %) (7)‡			
Unemployed	20 (33.3%)	8 (13.3%)	0.004~
Employed	8 (13.3%)	27 (45.0%)	0.001~
Students	25 (41.7)	25 (41.7)	0.575~

'P-values' *$=t$-test ~$=$Fisher's exact.
† 'White ethnicity' refers to subjects who are White British, White Irish, or other White backgrounds.
'Mixed ethnicity' refers to those who are White and Black Caribbean, mixed White and Black African, mixed White and Asian, or any other mixed backgrounds.
'Asian ethnicity'refers to those who are Indian or Chinese.
'Black ethnicity' refers to subject from any Black backgrounds.
‡ Occupational status is broadly categorised into three groups.
'Unemployed' includes subjects who do not have a job, either they are looking for work, not looking for work (e.g., housewife), or not being able to work due to medical reasons.
'Employed'refers to people who have full/part-time employment, or employed but currently unable to work.
'Students' refers to full/part-time students, including those who are also working some hours.

Table 2
Endorsement rates for each traumatic event and total number of times each trauma occurred for HR and HV participants.

Event	Endorsement rates for each traumatic event		Total N of times each trauma occurred		
	HR (%)	HV (%)	HR	HV	p-Value~
A really bad car, boat, train, or airplane accident	5 (8.3%)	6 (10.0%)	14	6	0.039
A really bad accident at work or home	10 (16.7%)	5 (8.3%)	21	8	0.007
A hurricane, flood, earthquake, tornado, or fire	2 (3.3%)	7 (11.7%)	2	14	0.018
Hit or kicked hard enough to injure – as a child	17 (28.3%)	7 (11.7%)	95	47	<0.001
Hit or kicked hard enough to injure – as an adult	14 (23.3%)	8 (13.3%)	83	18	<0.001
Forced or made to have sexual contact – as a child	5 (8.3%)	3 (5.0%)	14	4	0.013
Forced or made to have sexual contact – as an adult	5 (8.3%)	1 (1.7%)	11	2	0.015
Attack with a gun, knife, or weapon	14 (23.3%)	6 (10.0%)	24	7	0.001
During military service – seeing something horrible or being badly scared	0 (0%)	0 (0%)	0	0	1
Sudden death of close family or friend	23 (38.3%)	31 (51.7%)	47	53	0.833
Seeing someone die suddenly or get badly hurt or killed	17 (28.3%)	10 (16.7%)	32	10	<0.001
Some other sudden event that made you feel very scared, helpless, or horrified	23 (38.3%)	12 (20.0%)	58	16	<0.001
Sudden move or loss of home and possessions	7 (11.7%)	3 (5.0%)	13	3	0.011
Suddenly abandoned by spouse, partner, parent, or family	16 (26.7%)	5 (8.3%)	24	6	<0.001

~ $=$Fisher's exact.

higher the BDI and BAI scores. Trauma intensity was not correlated with BDI or BAI scores.

3.3.5. Number of traumas, trauma intensity and age at trauma exposure as predictors of HR

A logistic regression analysis was conducted to determine the impact of traumatic events, age at traumatic event or event intensity on the likelihood of being HR. In light of the significant differences between the groups in age at study entry, and because age might be related to number of events or age of trauma, age at study entry was entered as a covariate in the model. The results are presented in Table 4.

In support of our previous findings, intensity was not a statistically significant predictor of being HR. However, both age at traumatic event and number of traumatic events were statistically significant predictors. Every traumatic event (while all other variables in the model were held constant) represented an odds ratio of 1.11. Each year (while other variables in the model were held constant) represented a reduced likelihood that a participant will be HR by 0.873.

3.3.6. Transitions from high risk (HR) to first episode psychosis (FEP)

After more than 1 year of follow-up for each individual at HR in our sample, only six (10%) made a transition into FEP. None of the HR individuals from this cohort received antipsychotics during the follow-up period.

4. Discussion

The aim of this study was to determine whether number of traumatic events, perceived intensity of traumatic events or age at trauma exposure is more likely to be associated with HR mental states. To achieve this, the prevalence of past traumatic experiences and the constituent characteristics of those experiences were compared between samples of individuals at HR of developing psychosis and HVs.

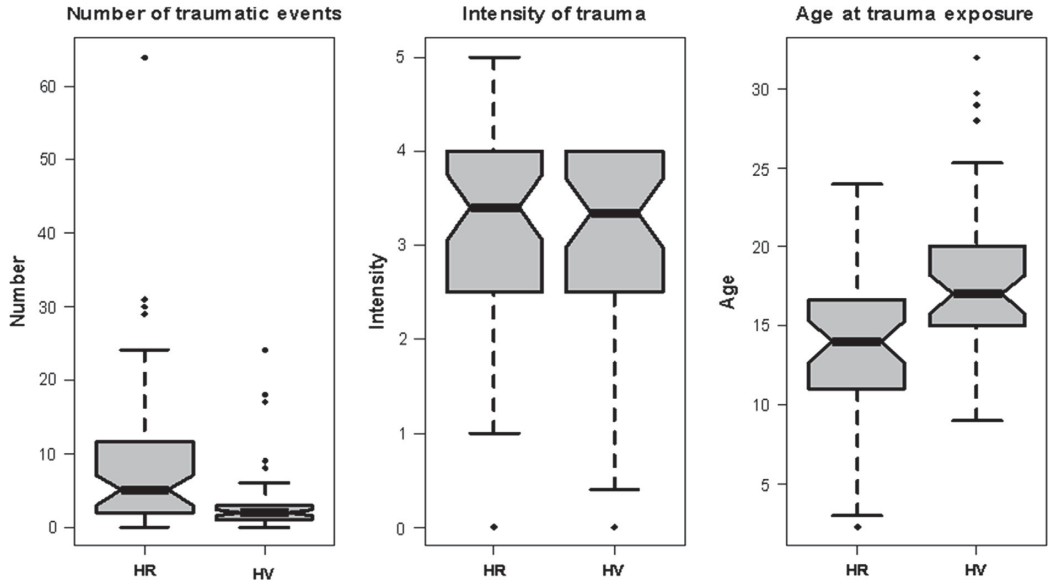


Fig. 1. Box plots to show the distribution of traumatic events, intensity of trauma and age at trauma exposure for HR and HV participants.

Table 3
Pearson correlation coefficients for the relationships between number of traumas, trauma intensity, age at trauma exposure, depression and anxiety for the whole sample.

	BAI	BDI	Number of traumas	Age at trauma exposure	Trauma intensity
BAI	1				
BDI	0.700**	1			
Number of traumas	0.470**	0.230*	1		
Age at trauma exposure	−0.380**	−0.350**	−0.170	1	
Trauma intensity	0.200	0.160	0.160	0.050	1

BDI-II = Beck Depression Inventory, Version II, BAI = Beck Anxiety Inventory.
* $p \leq 0.05$.
** $p \leq 0.001$.

Table 4
Summary of logistic regression analysis for variables predicting HR.

Parameter	Regression coefficient	Standard error	Wald *p*-value	Odds ratio	95% CI of odds ratio
Age	−0.147	0.063	0.019	0.863	(0.764, 0.976)
Number of traumas	0.104	0.045	0.019	1.11	(1.017, 1.211)
Age at trauma exposure	−0.135	0.067	0.042	0.873	(0.766, 0.995)
Trauma intensity	−0.04	0.206	0.848	0.961	(0.643, 1.438)

The finding that HR participants had both a higher incidence of trauma and reported repeated exposure to trauma than HVs supports the possibility of an association between trauma and psychotic-like symptoms. Several studies have reported that repeated exposure/increasing frequency is linked to stronger associations with sub-clinical psychotic symptoms (de Loore et al., 2007; Arseneault et al., 2011) and transitions to psychosis (Read et al., 2005; Thompson et al., 2009; Bechdolf et al., 2010). Another alternative explanation for these findings could be the role of the HR's individual behaviour in the occurrence of traumatic events. Kendler et al. (1999) reported the association between stressful life events and onset of depression can be explained by individuals selecting themselves into high risk situations. In concurrence, Stein et al. (2002) proposed that individual differences in personality influence environmental choices. These genetic factors can increase an individual's risk of exposure to some forms of trauma. Therefore, it is possible that the HR individuals in this study were more likely to self-select a high risk environment.

Traumatic events involving physical abuse with intention to harm accounted for the largest proportion of reported trauma for both groups and showed the largest differences between HV and HR participants. This supports previous conjecture that an element of threat, or a perception of threat, rather than the nature of the trauma (e.g., physical, sexual or emotional) could be more important in understanding any links between psychotic symptoms and trauma (Arseneault et al., 2011).

It is possible that this large difference can be explained by the conjecture that HR individuals are prone to paranoid thinking. Conversely, it has been suggested that beliefs about threat to the self can emerge as a response to interpersonal stress and trauma. Pre-existing negative beliefs about the self can combine with threatening appraisals of others resulting in anxiety. Feelings of threat and paranoia ensue leading to an increased likelihood of persecutory delusions (Freeman et al., 2002). Furthermore, anxiety has been shown to be predictive of the occurrence of paranoid thoughts (Freeman et al., 2008) and of the persistence of persecutory delusions (Startup et al., 2007). Indeed, Freeman and Fowler (2009) proposed that trauma influences persecutory thinking non-specifically via the creation of anxiety. This association between negative beliefs about self and others, anxiety and paranoia is supported by the high levels of anxiety in this study's HR group.

Associations between trauma and psychotic symptoms have also been found for emotional and physical trauma (Read et al., 2005), with more severe trauma (e.g. sexual) displaying the strongest associations (Read et al., 2005; Bechdolf et al., 2010; Thompson et al., 2014).

Conversely, in the present study, events involving sexual abuse were comparatively low for both groups: 16.6% in HR and 6.6% in

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

HV. Two recent studies reported much higher rates of 27% and 28% in samples at clinical high risk for psychosis (Thompson et al., 2009; Bechdolf et al., 2010). This was particularly notable considering the age range of the participants in the present study was 10 years greater than these two studies. Indeed, Bechdolf et al. (2010) found that history of sexual trauma predicted conversion to psychotic disorder. Even longitudinal data from individuals at HR suggested a relationship between experience of sexual abuse and the medium-to-long term development of a psychotic disorder (Thompson et al., 2014). It could be argued that lack of sexual abuse in the present study may be an ameliorating factor against transition.

Results showed that although HR participants experienced significantly more traumatic events than HVs, they did not report any more distress in relation to these events. Despite 60–70% of all individuals reporting distress in response to traumatic events, it is of note that, for both groups, 30–40% of traumatic experiences were not judged to be emotionally distressing. This was corroborated by the presence of only a single case of PTSD in the whole sample. An explanation of this finding is that because HR individuals are exposed to more recurrent traumatic events, they have become more desensitised to the impact and therefore, the threshold for distress associated with the events is reduced. This may go some way to explaining their greater risk of exposure. Another consideration is the possibility that the perceived intensity of trauma is a future predictor of psychopathology other than psychosis. This highlights the relevance of understanding the emotional impact of trauma on the subjective perceptions of the individual which can extend our understanding of why particular events cause traumatic stress in particular individuals.

First incidents of trauma and total number of traumas occurred at earlier ages for HR participants and HR participants experienced significantly more traumas during the developmental period between the ages 0 and 8 years. To date, there has been no conclusive research identifying the most vulnerable developmental period for the risk-increasing effects of trauma (Wigman et al., 2012b) and previous studies have found that the cumulative effect of trauma during early to late childhood, rather than the timing, confers the highest risk for developing psychotic symptoms (Arseneault et al., 2011).

A key finding of the current study was that both incidences of trauma and age at which trauma occurred were the most likely predictors of becoming HR, not the degree of distress reported as result of the trauma. Certainly, previous studies have consistently found strong associations with early childhood trauma and psychotic symptoms (Freeman and Fowler, 2009; Arseneault et al., 2011) and it has been suggested that this is because young children may lack the coping strategies needed to deal with the consequences of experiencing trauma (Arseneault et al., 2011). In this study the higher instances of trauma occurred between 9 and 24 years rather than 0 and 8 years. Also, the median age for first trauma was 9 and for all traumas 14. In light of previous findings, it is possible to interpret this lack of earlier trauma as another ameliorating factor against transition to full psychosis, although a longitudinal design would be necessary to substantiate this. Similarly, previous research revealed a high prevalence of trauma in patient cohorts with established psychotic disorder (Read et al., 2005) and in those at risk of developing psychosis (Thompson et al., 2014). Also, associations have been reported between numbers of traumatic events and clinically high risk samples in recent studies, reporting a 97% and 69.6% prevalence rate of at least one trauma (Thompson et al., 2009; Bechdolf et al., 2010), although incidence of successive trauma was not delineated in either of these studies. Nevertheless, it has been shown that the accumulation of trauma increases the risk to develop subclinical psychotic experiences in a dose–response fashion (de Loore et al., 2007). This seems to suggest that, in this study, regardless of the subjectively perceived distress as result of the trauma, both higher incidents of trauma and younger ages at trauma exposure increased the likelihood of being at HR. Higher ages for trauma exposure and lack of sexual abuse could be ameliorating factors for the HR individuals in this study.

Previous research has found the majority of help-seeking individuals at HR initially present with anxiety disorder or major depression (Velthorst et al., 2009; Addington et al., 2011; Wigman et al., 2012a; Hui et al., 2013) and the association of trauma and paranoia can be explained by levels of anxiety (Freeman and Fowler, 2009). The high levels of anxiety and depression found in our HR group replicate these findings. Combined with the very low transition rates to date, our low initial conversion rate adds credence to the argument that there is a lack of diagnostic specificity and predictive value in the HR model. Therefore, it is possible to speculate that a HR mental state is not a specific marker for psychosis. Supplement this with the prevalent co-presence of anxiety and depression in this group, it is feasible to consider that trauma may play a role in this manifestation of symptoms. Indeed, other authors (Spauwen et al., 2006) have also speculated that exposure to trauma may be a hidden factor explaining a substantial part of the morbidity associated with sub-clinical psychosis. This is especially pertinent in light of recent research that suggests the incidence of psychotic experiences decreases significantly when exposure to trauma ceases (Kelleher et al., 2013).

The low transition rates could be explained by the short follow up in this study. The risk for transition is highest in the first 2 years, but transitions can occur up to at least 10 years after presentation (Nelson et al., 2013). Alternatively, it is possible to consider the lack of transitions as an indicator that trauma is not a predictor of psychosis. Therefore, if traumatic experiences are considered as a non-specific marker of psychopathology, their consideration and assessment become paramount. As Carlson et al. (2013) emphasised, traumatic events may not directly cause symptoms, but may precipitate mental disorder in individuals who are vulnerable because of previous, existing or later biological, psychological or social factors. Conversely, a recent study looking at childhood adversity, including diverse events such as separation and abuse, concluded that the combination of childhood abuse and exposure to further stressors establishes an enduring susceptibility to psychosis (Morgan et al., 2014). This accentuates the importance of a detailed consideration of potentially traumatic life events during clinical assessment. The presence of these events combined with the subjective interpretation could be related to the experience of psychotic or psychotic-like phenomena.

There is debate around the events that are included in the measurement of trauma. McNally (2009) has expressed concern that including non-catastrophic events in trauma scales creates an excessively broad definition of a traumatic event, resulting in increased numbers of PTSD diagnoses based on exposure to relatively minor stressors. Shalev and Ursano (2003) contended that if traumatic stressors are only distinguished by perceived threat of injury or death, the essential nature of human traumatisation is lost. They argued that treat is not a necessary condition for being traumatised and elements such as separation, relocation, loss, isolation and uncertainty can be traumatising. Other authors agree, positing that the defining features of traumatic events are negative valence, lack of controllability and suddenness (Carlson and Dalenberg, 2000). Therefore, the authors of the THS maintain that also assessing events involving severe emotional loss or pain such as 'sudden move or loss of home' and 'possessions and sudden abandonment by family or loved ones' is valid. These events have been associated with post-traumatic symptoms as strongly as Criterion A stressors (Carlson et al., 2013; Van Hooff et al., 2009). Such experiences are common for refugees, survivors of natural disasters and war, and for children in low socioeconomic status families (Carlson et al., 2011). We felt that

inclusion of these items in the present study was justified as HR cohorts can have comparable experiences.

Notwithstanding the strengths of this study, the results must be interpreted in light of the following limitations. First, the healthy volunteers were statistically significantly older than the high risk participants and this might be interrelated with number of events or age of trauma. However, HR participants still had higher amounts of trauma at younger ages. It is possible that were the groups of a similar age, the differences would only have been greater between the two groups. To adjust for this, age at study entry was entered as a covariate in the logistic regression model. Second, our findings are based on self-report. It is possible that the HR mental state may lead to inaccuracy in the recall and reporting of traumatic experiences. Trauma was measured by the respondent's subjective information and not corroborated by independent information; therefore it was not possible to ascertain if trauma was under or overestimated. However, research has shown that even individuals with psychotic disorders can be as accurate in recalling traumatic experiences as a population sample (Kelleher et al., 2013). Conversely, confidential self-report produces twice the number of childhood traumas reported compared with a psychiatric interview (Dill et al., 1991). This indicates that including a combination of methods would yield the most accurate record of trauma. Third, only a crude, one-item measure of distress was used in this study. Future research should include a valid measure to elucidate any relationships between distress, trauma, anxiety and psychotic experiences/symptoms. Fourth, although the THS (Carlson et al., 2011) does examine trauma involving physical abuse as a child and events that induce feelings of fear, helplessness and horror there is no specific question concerning bullying. It is possible that a large proportion of traumatic experiences were missed due to this omission; particularly as research has found an elevated risk for psychosis among bullied children (Arseneault et al., 2011; Addington et al., 2013). Fifth, the study is cross-sectional; without further longitudinal data it is not possible to fully ascertain particular trauma characteristics as predictors of conversion to psychosis or as a contributing factor to HR mental states. Finally, there was no clear definition between the measurement of actual trauma and stressful life events. This may account for the high prevalence of reported trauma in our sample. However, an objective of the THS is to provide substantial information about exposure to *potentially* traumatic stressors and responses to stressors. Furthermore, we considered it important to include all events that individuals identified as traumatic, as the accumulation of these events may have an impact on the development of psychotic-like experiences as proposed by Morgan et al. (2014). Life stressors as well as true trauma are important considerations in developing psychopathology, irrespective of the character of the psychotic phenomenon.

Our work adds to the literature concerning the understanding of trauma in HR mental states. It emphasises the clinical importance of thoroughly assessing trauma characteristics in individuals at clinical HR in order to enable differentiation between psychotic-like experiences that may reflect dissociative responses to trauma and genuine prodromal psychotic presentations. Subsequently, this will help understand the links between traumatic events, psychotic-like symptoms and other non-psychotic psychiatric disorders, such as depression and anxiety.

Funding

This work was supported by the National Institute for Health Research (NIHR; programme grant RP-PG-0606-1335 'Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses' awarded to P.B.J.). The work forms part of the NIHR Collaboration for Leadership in Applied Health Research & Care for Cambridgeshire & Peterborough (CLAHRC-CP). The NIHR had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

The authors have not transmitted any conflicts of interest based on business relationships of their own or of immediate family members.

Acknowledgements

The authors thank the PAATh Study team (Gillian Shelley, Chris McAlinden, Carolyn Crane and Gerhard Smith) and all members of CAMEO services for their help and support with this study.

References

Addington, J., Stowkowy, J., Cadenhead, K.S., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Cannon, T. D., 2013. Early traumatic experiences in those at clinical high risk for psychosis. Early Intervention in Psychiatry 7 (3), 300–305.

Addington, J., Cornblatt, B.A., Candenhead, K.S., Cannon, T.D., McGlashan, T., Perkins, D.O., Seidman, L., Tsuang, M.T., Walker, E.F., Woods, S., Heinssen, R., 2011. At clinical high risk for psychosis: outcome for nonconverters. American Journal of Psychiatry 168, 800–805.

Arseneault, L., Cannon, M., Fisher, H.L., Polanczyk, G., Moffitt, T.E., Caspi, A., 2011. Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. American Journal of Psychiatry 168, 65–72.

Bebbington, P., Jonas, S., Kuipers, E., King, M., Cooper, C., Brugha, T., Meltzer, H., McManus, S., Jenkins, R., 2011. Childhood sexual abuse and psychosis: data from a cross-sectional national psychiatric survey in England. The British Journal of Psychiatry 199, 29–37.

Bechdolf, A., Stompson, A., Nelson, B., Cotton, S., Simmons, M.B., Amminger, G.P., Leicester, S., Francey, S.M., McNab, C., Krstev, H., Sidis, A., McGorry, P.D., Yung, A.R., 2010. Experience of trauma and conversion to psychosis in an ultra-high-risk (prodromal) group. Acta Psychiatrica Scandinavica 121, 377–384.

Beck, A.T., Steer, R.A., Ball, R., Ranieri, W., 1996. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. Journal of Personality Assessment 67 (3), 588–597.

Beck, A.T., Steer, R.A., 1993. Beck Anxiety Inventory Manual. Harcourt Brace and Company, San Antonio.

Bendall, S., Jackson, H.J., Hulbert, C.A., McGorry, P.D., 2008. Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. Schizophrenia Bulletin 34, 568–579.

Carlson, E.B., Smith, S.R., Palmieri, P.A., Dalenberg, C., Ruzek, J.I., Kimerling, R., Burling, T.A., Spain, D.A., 2011. Development and validation of a brief self-report measure of trauma exposure: the Trauma History Screen. Psychological Assessment 23 (2), 463–477.

Carlson, E.B., Dalenberg, C., 2000. A conceptual framework for the impact of traumatic experiences. Trauma, Violence, and Abuse 1, 4–28.

Carlson, E.B., Smith, S.R., Dalenberg, C.J., 2013. Can sudden, severe emotional loss be a traumatic stressor? Journal of Trauma & Dissociation 14 (5), 519–528.

Cheng, F., Kirkbride, J.B., Lennox, B.R., Perez, J., Masson, K., Lawrence, K., Hill, K., Feeley, L., Painter, M., Murray, G.K., Gallagher, O., Bullmore, E.T., Jones, P.B., 2011. Administrative incidence of psychosis assessed in an early intervention service in England: first epidemiological evidence from a diverse, rural and urban setting. Psychological Medicine 41 (5), 949–958.

de Loore, E., Drukker, M., Gunther, N., Feron, F., Deboutte, D., Sabbe, B., Mengelers, R., van Os, J., Myin-Germey, I., 2007. Childhood negative experiences and subclinical psychosis in adolescents: a longitudinal general population study. Early Intervention in Psychiatry 1, 201–207.

Dill, D.L., Chu, J.A., Grob, M.C., Eisen, S.V., 1991. The reliability of abuse history reports: a comparison of two inquiry formats. Comprehensive Psychiatry 32, 166–169.

Fisher, H.L., Jones, P.B., Fearon, P., Craig, T.K., Dazzan, P., Morgan, K., Hutchinson, G., Doody, G.A., McGuffin, P., Leff, J., Murray, R.M., Morgan, C., 2010. The varying impact of type, timing and frequency of exposure to childhood adversity on its association with adult psychotic disorder. Psychological Medicine 40, 1967–1978.

Freeman, D., Fowler, D., 2009. Routes to psychotic symptoms: trauma, anxiety and psychosis like experiences. Psychiatry Research 169 (2), 107–112.

Freeman, D., Pugh, K., Antley, A., Slater, M., Bebbington, P., Gittins, M., Dunn, G., Kuipers, E., Fowler, D., Garety, P., 2008. A virtual reality study of paranoid thinking in the general population. British Journal of Psychiatry 192, 258–263.

Freeman, D., Garety, P., Kuipers, E., Fowler, D., Bebbington, P., 2002. A cognitive model of persecutory delusions. British Journal of Clinical Psychology 41, 331–347.

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Hui, C., Morcillo, C., Russo, D.A., Stochl, J., Shelley, G.F., Painter, M., Jones, P.B., Perez, J., 2013. Psychiatric morbidity and disability in young people at clinical high risk for psychosis. Schizophrenia Research 48 (1–3), 175–180.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13 (2), 261–276.
Kelleher, I., Keeley, H., Corcoran, P., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2013. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. American Journal of Psychiatry 170, 734–741.
Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., Molloy, C., Roddy, S., Clarke, M.C., Harley, M., Arseneault, L., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2012. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. British Journal of Psychiatry 1, 26–32.
Kendler, K.S., Karkowski, L.M., Prescott, C.A., 1999. Causal relationship between stressful life events and the onset of major depression. American Journal of Psychiatry 156, 837–841.
Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean? Schizophrenia Research 79 (2–3), 231–238.
McNally, R.J., 2009. Can we fix PTSD in DSM-V? Depression and Anxiety 26, 597–600.
Morgan, C., Kirkbride, J., Leff, J., Craig, T., Hutchinson, G., McKenzie, K., Morgan, K., Dazzan, P., Doody, G.A., Jones, P., Murray, R., Fearon, P., 2007. Parental separation, loss and psychosis in different ethnic groups: a case-control study. Psychological Medicine 37, 495–503.
Morgan, C., Reininghaus, U., Reichenberg, A., Frissa, S., SELCoH study teamHotopf, M., Hatch, S.L., 2014. Adversity, cannabis use and psychotic experiences: evidence of cumulative and synergistic effects. British Journal of Psychiatry 204, 346–353.
Nelson, B., Yuen, H., Wood, S.J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D.L., Brewerm, W.J., Francey, S.M., Amminger, G.P., Thompson, A., McGorry, P.D., Yung, A.R., 2013. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. Journal of the American Medical Association Psychiatry 70 (8), 793–802.
Norris, F.H., Hamblen, J.L., 2004. Standardized self-report measures of civilian trauma and PTSD. In: Wilson, J., Keane, T.M. (Eds.), Assessing Psychological Trauma and PTSD. The Guilford Press, New York, pp. 63–102.
Read, J., van Os, J., Morrison, A.P., Ross, C.A., 2005. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatrica Scandinavica 112, 330–350.
R Core Team, 2013. (URL). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Shalev, A.Y., Ursano, R.J., 2003. Mapping the multidimensional picture of acute responses to traumatic stress. In: Orner, R., Schnyder, U. (Eds.), Reconstructing Early Intervention After Trauma. Oxford University Press, Oxford, England, pp. 228–235.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiler, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry 59 (20), 22–33.
Spauwen, J., Krabbendam, L., Lieb, R., Wittchen, H.U., van Os, J., 2006. Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. British Journal of Psychiatry 188, 527–533.
Startup, H., Freeman, D., Garety, P.A., 2007. Persecutory delusions and catastrophic worry in psychosis: developing the understanding of delusion distress and persistence. Behaviour Research and Therapy 45, 523–537.
Stein, M.B., Lang, K.L., Taylor, S., Vernon, P.A., Livesley, W.J., 2002. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. American Journal of Psychiatry 159, 1675–1681.
Thompson, A.D., Nelson, B., Yuen, H.P., Lin, A., Amminger, G.P., McGorry, P.D., Wood, S.J., Yung, A.R., 2014. Sexual trauma increases the risk of developing psychosis in an ultra high-risk "prodromal" population. Schizophrenia Bulletin 40 (3), 697–706.
Thompson, J.L., Kelly, M., Kimhy, D., Harkavy-Friedman, J.M., Khan, S., Messinger, J. W., Schobel, S., Goetz, R., Malaspina, D., Corcoran, C., 2009. Childhood trauma and prodromal symptoms among individuals at clinical high risk for psychosis. Schizophrenia Research 108, 176–181.
Tikka, M., Luutonen, S., Ilonen, T., Tuominen, L., Kotimäki, M., Hankala, J., Salokangas, R.K.R., 2013. Childhood trauma and premorbid adjustment among individuals at clinical high risk for psychosis and normal contral subjects. Early Intervention in Psychiatry 7, 51–57.
Van Hooff, M., McFarlane, A.C., Baur, J., Abraham, M., Barnes, D.J., 2009. The stressor Criterion-A1 and PTSD: a matter of opinion? Journal of Anxiety Disorders 23, 77–86.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophrenia Bulletin 38, 661–671.
Velthorst, E., Nieman, D.H., Becker, H.E., van de Fliert, R., Dingemans, P.M., Klaassen, R., de Haan, L., van Amelsvoort, T., Linszen, D.H., 2009. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophrenia Research 109, 60–65.
Wigman, J.T.W., van Nierop, M., Vollebergh, W.A., Lieb, R., Beesdo-Baum, K., Wittchen, H.U., van Os, J., 2012a. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity—implications for diagnosis and ultra-high risk research. Schizophrenia Bulletin 38 (2), 247–257.
Wigman, J.T.W., van Winkel, R., Ormel, J., Verhulst, F.C., van Os, J., Vollebergh, W.A. M., 2012b. Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence. Acta Psychiatrica Scandinavica 126 (4), 266–273.
Yung, A.R., Yuen, H.P., Berger, G., Francey, S., Hung, T.C., Nelson, B., Phillips, L., McGorry, P., 2007. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophrenia Bulletin 33 (3), 673–681.
Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S. M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Australian and New Zealand Journal of Psychiatry 39 (11–12), 964–971.
Zimbron, J., Ruiz de Azua, S., Khandaker, G.M., Gandamaneni, P.K., Crane, C.M., González-Pinto, A., Stochl, J., Jones, P.B., Pérez, J., 2012. Clinical and sociodemographic comparison of people at high-risk for psychosis and with first-episode psychosis. Acta Psychiatrica Scandinavica 127 (3), 210–216.

Appendix 12 First-rank symptoms and premorbid adjustment in young individuals at increased risk of developing psychosis

Original Paper

Psychopathology

Psychopathology
DOI: 10.1159/000369859

Received: July 22, 2014
Accepted after revision: November 10, 2014
Published online: February 18, 2015

First-Rank Symptoms and Premorbid Adjustment in Young Individuals at Increased Risk of Developing Psychosis

Carmen Morcillo[a, b] Jan Stochl[d] Debra A. Russo[a, b] Antonio Zambrana[e]
Navanthi Ratnayake[b] Peter B. Jones[a–c] Jesus Perez[a, b]

[a]Department of Psychiatry, University of Cambridge, [b]CAMEO Early Intervention in Psychosis Service, CPFT, and [c]NIHR Collaboration for Leadership in Applied Health Research and Care, Cambridge, and [d]Department of Health Sciences, University of York, York, UK; [e]Department of Psychiatry, University of Salamanca, Salamanca, Spain

Key Words
At-risk mental state · Early intervention · First-rank symptoms · Premorbid adjustment · Psychosis · Risk · Schizophrenia

Abstract
Background: Individuals at clinical high risk (CHR) for psychosis represent a heterogeneous group with a high rate of comorbid psychiatric disorders. There is little information on whether certain qualitative aspects of psychotic symptoms among CHR individuals may be predictive of future psychosis. This study focused on describing the prevalence of first-rank symptoms (FRS) among a sample of CHR individuals and its association with future transition to psychosis and, from a neurodevelopmental perspective, the level of adjustment of individuals at CHR during their childhood was also analysed. ***Sampling and Methods:*** Participants comprised 60 individuals at CHR (according to the Comprehensive Assessment of At-Risk Mental States, CAARMS) at the time of their referral to an early intervention service and 60 healthy volunteers (HVs). All subjects were assessed by senior research clinicians using the Mini International Neuropsychiatric Interview (MINI), and the Positive and Negative Syndrome Scale (PANSS). FRS were defined according to Kurt Schneider's original classification, and information was collected from PANSS, CAARMS and clinical reports. Early premorbid functioning was measured using the Premorbid Adjustment Scale (PAS). We grouped individuals by number and type of FRS and analysed transitions to full-blown psychosis over a 2-year follow-up period. We also correlated the general social and functional adjustment of these individuals during their childhood (6–11 years of age) with the future development of mental states at CHR and FRS. ***Results:*** Over 69% of CHR individuals had more than one DSM-IV psychiatric diagnosis, mainly within the affective and anxiety diagnostic spectra. At least one FRS was present in 43.3% of CHR individuals, and 21.6% of these had more than one. Auditory hallucinations and passivity experiences were the most commonly reported. Only 10% of individuals at CHR made a transition to first-episode psychosis (FEP) over 2 years and, except for passivity experiences, the presence of one or more FRS was not significantly associated with the transition to FEP. CHR individuals, especially those with FRS, had poorer premorbid functioning and adjustment as children across educational, social and peer relationship domains than HVs. However, this was not associated with FEP 2 years later. ***Conclusions:*** FRS might not be indicators of psychosis alone but of different psychiatric disorders. In line with the neurodevelopmental model of psychosis, individuals at CHR might

KARGER 125

E-Mail karger@karger.com
www.karger.com/psp

© 2015 S. Karger AG, Basel
0254–4962/15/0000–0000$39.50/0

Karger Open access

This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

Jesus Perez
Block 7, Ida Darwin Site
Fulbourn Hospital
Fulbourn, Cambridge CB21 5EE (UK)
E-Mail jp440@cam.ac.uk

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/16/2015 4:02:26 PM

© 2015 S. Karger AG, Basel. This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

be exhibiting several vulnerability traits and manifestations of abnormal developmental processes that might predict a future psychiatric disorder and/or long-term impairment.

© 2015 S. Karger AG, Basel

Introduction

Individuals at clinical high risk (CHR) for psychosis represent a heterogeneous group where psychotic experiences are associated with a wide range of psychopathology, lacking the specificity and predictive validity to indicate a transition to psychosis [1, 2]. Recent longitudinal studies among individuals at CHR have reported transition rates to full-blown psychosis of between 7 and 54% [3]. While the clinical signs and symptoms among individuals at CHR have been widely studied at a dimensional level [4–6], few studies have evaluated possible qualitative aspects of positive psychotic symptoms that might predict poorer outcomes and/or conversion to psychosis [4].

Among positive symptoms, Kurt Schneider (1887–1967) defined 'first-rank symptoms' (FRS) as those that, despite not being pathognomonic, might have a decisive weight in differentiating schizophrenia from other mental disorders [7]. Further research has confirmed that FRS are not only common in schizophrenia [8, 9] but also in other severe non-schizophrenic [10] and affective psychoses [11]. Whereas discriminatory symptoms have not yet been found for individuals at CHR, one question that remains unanswered relates to whether FRS, when present among CHR individuals, could be a negative indicator and predictor of future transition towards full-blown psychosis.

On the other hand, it has been widely documented that negative symptoms and, in particular, poor premorbid adjustment and functioning are early indicators of psychotic illness [12–14]. Several studies have reported low levels of functioning among individuals who are at CHR or during the premorbid phase of psychosis [14, 15]. However, from a developmental perspective, an issue that remains elusive is whether individuals at CHR and with FRS may present with a lower level of functioning at earlier stages of life, indicating a more severe developmental course over time.

Therefore, the goal of our study was 3-fold. Based on a sample of individuals at CHR who were referred to an early intervention in psychosis service and healthy volunteers (HVs) recruited from the same geographical area, we aimed to describe the following: (1) the prevalence of FRS among individuals at CHR, (2) the association between FRS and transition to full-blown psychosis and (3) the level of adjustment of individuals at CHR and with FRS during their childhood (6–11 years of age) in terms of social and academic functioning.

Methods

We explored the presence of FRS among a sample of 60 individuals at CHR at the time of their referral to an early intervention service and 60 HVs. We grouped individuals by number and type of FRS and analysed transitions to full-blown psychosis over a 2-year follow-up period. We then correlated the general social and functional adjustment of these individuals during their childhood (6–11 years of age) with the future development of mental states at CHR and FRS.

Setting

CAMEO (http://www.cameo.nhs.uk) is an early intervention in psychosis service offering management for people aged 14–35 years suffering from first-episode psychosis (FEP) in Cambridgeshire, UK. CAMEO also accepts referrals of people at CHR. Referrals are accepted from multiple sources, including general practitioners, other mental health services, school and college counsellors, relatives, and self-referrals [1].

Sample

A consecutive cohort of 60 help-seeking individuals (aged 16–35 years) referred to CAMEO from February 2010 to September 2012 met the criteria for CHR, according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) [16]. Referrals came to our offices via a number of different routes, including self-referral, carers and relatives and schools and colleges, but mainly via primary care. All individuals identified as high risk for psychosis living and detected in Cambridgeshire and Peterborough were offered a systematic follow-up in the context of a prospective, naturalistic study called PAATH (Prospective Analysis of At-Risk Mental States and Transitions into Psychosis). Participants were followed up for 2 years from the initial referral date. During this period, they were asked to attend subsequent interviews where they completed structured interviews and questionnaires. In our sample, all individuals fulfilled the criteria for the attenuated psychotic symptoms group. In addition, 7 individuals (11.7%) also qualified for the vulnerability traits group (individuals with a family history of psychosis in a first-degree relative or schizotypal personality disorder plus a 30% drop in GAF score from premorbid level, sustained for a month, occurring within the previous 12 months or GAF score of 50% or less for the previous 12 months). Intake exclusion criteria were as follows: (1) acute intoxication or withdrawal associated with drug or alcohol abuse or any delirium, (2) confirmed intellectual disability (Wechsler Adult Intelligence Scale – tested IQ <70) or (3) prior total treatment with antipsychotics for more than 1 week.

During the same period (February 2010 to September 2012), a random sample of 60 HVs was recruited by post, using the PAF® (Postal Address File) provided by Royal Mail, UK. To ensure that each CHR and HV resided in the same geographical location, 50

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/18/2015 4:02:28 PM

corresponding postcodes, matching the first 4/5 characters and digits of each recruited CHR participant (e.g. PE13 5; CB5 3), were randomly selected using Microsoft SQL Server, a relational database management system, in conjunction with the PAF database. Each of these 50 addresses was sent a recruitment flyer containing a brief outline of the study, inclusion criteria and contact details. If this failed to generate recruits, a consecutive sample of postcodes would be selected. This process was repeated until a match was recruited. An average of 100 flyers was sent to each postcode to recruit the 60 HVs. HVs interested in the study could only participate if they were aged 16–35 years, resided in the same geographical area as CHR participants (Cambridgeshire) and did not have previous contact with mental health services.

Ethical Approval

Ethical approval was granted by the Cambridgeshire East Research Ethics Committee.

Measures

All participants were assessed with sociodemographic (age, gender, ethnicity and occupational status) and several clinical measures at the time of their referral to CAMEO. The assessments were carried out by senior research clinicians trained in each of the measurement tools.

CHR participants were interviewed by senior trained psychiatrists working in CAMEO, using the Mini International Neuropsychiatric Interview (MINI), version 6.0.0 [17] – a brief structured diagnostic interview for DSM-IV Axis I psychiatric disorders. The Positive and Negative Syndrome Scale (PANSS) [18] for psychotic symptoms was employed to capture the severity of positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items) in a 7-point scale, with higher scores indicating greater severity of illness. Summary score and sub-domain scores of positive, negative and general psychopathology symptoms were computed. HVs were also assessed by senior researcher clinicians using the PANSS and CAARMS. All the assessments, including the CAARMS, were performed by the same assessor for each participant.

FRS were defined according to Kurt Schneider's original classification [7]. These included the following: (1) auditory hallucinations (hearing voices conversing with one another, voices heard commenting on one's actions and thought echo); (2) somatic hallucinations; (3) passivity experiences (delusions of control/being controlled); (4) thought withdrawal; (5) thought insertion; (6) thought broadcasting, and (g) delusional perceptions.

The existence and description of any of these symptoms was documented on the PANSS, CAARMS and clinical reports by experienced research clinicians working at CAMEO. The clinical assessments were supervised by senior consultant psychiatrists. For the purpose of this study, 2 blinded independent psychiatrists also gathered specific information related to FRS collected from the above-mentioned sources. Co-coding was then discussed with a senior consultant psychiatrist with expertise in psychosis.

The Premorbid Adjustment Scale (PAS) comprises 36 items describing levels of functioning before the onset of psychosis. These items cover sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and capacity to establish socio-sexual relationships, assessed during four periods in life: childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood (19 years and beyond) [19]. The rating is based on interviews with the patient and/or with family members. The scoring range of each item is 0–6, with 0 indicating the best level of functioning and 6 the worst. We assessed premorbid functioning and adjustment during childhood (up to 11 years of age), and therefore the domain related to socio-sexual relationships was not included. We obtained mean scores for each of the other four domains.

Statistical Analysis

Our primary method for comparison of categorical sociodemographic variables between individuals at CHR and HVs was Fisher's exact test. For age comparison the t test was used. We also employed Fisher's exact test to analyse associations between the presence of FRS in CHR individuals and transitions to psychosis. The Wilcoxon signed-rank test was used to compare PAS domains between CHR individuals and HVs. All computations were performed using R software [20].

Results

Sociodemographic Profile

Sociodemographic information was collected, comprising age, gender, ethnicity, and occupational status. Table 1 shows a comparison between CHR individuals and HVs. There was a difference in age between the two groups; HVs were significantly older than the CHR participants ($p \leq 0.001$). The CHR group had a slightly higher proportion of males and the HV group had a slightly higher proportion of females. Both groups were predominantly White with a similar proportion of mixed, Asian and Black participants. Both groups contained the same number of students (41.7%), but significantly more HV participants were employed ($p = 0.001$).

DSM-IV Diagnoses and PANSS Scores

We obtained MINI DSM-IV diagnoses for 55 of the 60 CHR individuals. Of these, 38 (69.1%) had more than one DSM-IV psychiatric diagnosis, mainly within the affective and anxiety diagnostic spectra. Primary diagnoses for this group were ranked in terms of frequency, as follows: major depressive episode, current or recurrent (n = 26; 47.3%) > social phobia (n = 7; 12.7%) = generalised anxiety disorder (n = 7; 12.7%) > obsessive compulsive disorder (n = 5; 9.1%) > bipolar disorder, type II (n = 2; 3.6%) > panic disorder (n = 1; 1.8%) = posttraumatic stress disorder (n = 1; 1.8%). Overall, 6 CHR individuals (10.9%) did not fulfil sufficient criteria for a DSM-IV Axis I diagnosis.

The mean PANSS scores for the CHR group comprised positive symptoms (13.1, SD = 3.2), negative symptoms (12.4, SD = 5.0) and general psychopathology (32.7, SD = 7.0). These scores indicated a 'mildly ill'

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/18/2015 4:02:28 PM

© 2015 S. Karger AG, Basel. This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

Table 1. Sociodemographic comparison between CHR individuals and HVs

Sociodemographic characteristics	CHR (n = 60)	HVs (n = 60)	p values
Age at study entry, years			<0.001
Median	19.89	22.60	
SD	2.38	5.68	
Minimum	16.41	16.18	
Maximum	30.21	35.57	
Gender, n			
Male	31 (51.7%)	26 (43.3%)	0.465
Female	29 (48.3%)	34 (56.7%)	0.465
Ethnicity, n			
White	56 (93.3%)	55 (91.7%)	1.000
Mixed	2 (3.3%)	2 (3.3%)	1.000
Asian	1 (1.7%)	2 (3.3%)	1.000
Black	1(1.7%)	1(1.7%)	1.000
Occupational status[a]			
Unemployed	20 (33.3%)	8 (13.3%)	0.004
Employed	8 (13.3%)	27 (45.0%)	0.001
Students	25 (41.7)	25 (41.7)	0.575

White ethnicity: subjects who were White British, White Irish or other White backgrounds. Mixed ethnicity: subjects who were White and Black Caribbean, mixed White and Black African, mixed White and Asian, or any other mixed backgrounds. Asian ethnicity: subjects who were Indian or Chinese. Black ethnicity: subjects from any Black backgrounds.

Occupational status was broadly categorized into 3 groups. Unemployed: subjects who did not have a job – those either looking for work, not looking for work (e.g. housewife) or not able to work due to medical reasons. Employed: people with full/part-time employment or those who were employed but currently unable to work. Students: full/part-time students, including those also working some hours.

p values: Fisher's exact test, except for age comparison (t test).

[a] Data on occupational status were missing for 7 participants.

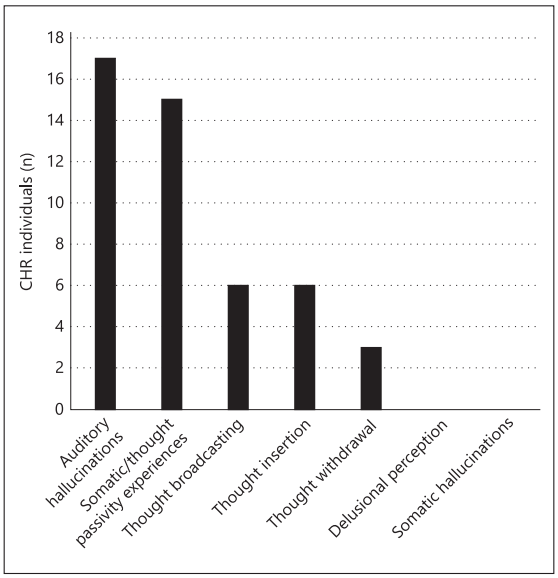


Fig. 1. Distribution and frequency of FRS in CHR individuals.

group with regards to psychotic symptoms [21]. PANSS scores for HVs were 7.1 (SD = 0.4) for positive symptoms, 7.8 (SD = 0.8) for negative symptoms and 16.4 (SD = 1.3) for general psychopathology. None of the HVs fulfilled CAARMS criteria for CHR.

Frequency of FRS and Associations with Transitions

The presence of any or more than one FRS was significantly higher among those individuals at CHR compared to HVs, who did not report FRS in our sample ($p < 0.001$). A total of 26 individuals at CHR (43.3%) presented at least one FRS, and 21.6% of them (n = 13) presented more than one. Among the different FRS, auditory hallucinations (mainly voices conversing with one another or commenting on one's actions) were the most frequently reported (28.3%) followed by passivity experiences (25%), thought broadcasting (10%), thought insertion (8.3%), and thought withdrawal (5%). Individuals at CHR in our sample did not report any somatic hallucination or delusional perception (fig. 1).

In our sample, only 6 (10%) individuals at CHR made a transition to FEP over 2 years, according to the

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/18/2015 4:02:28 PM

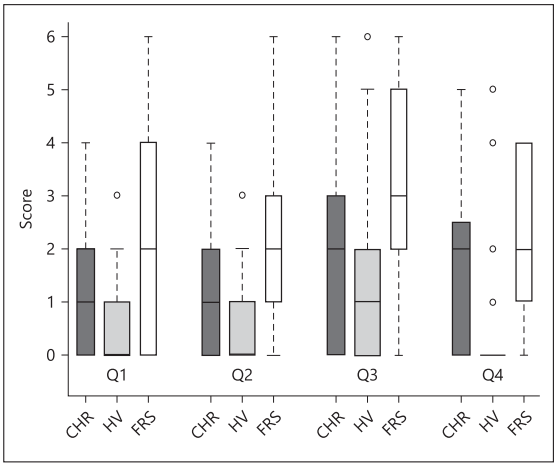


Fig. 2. Comparison of PAS domains (6–11 years of age) between CHR individuals, HVs and a subgroup of CHR individuals with FRS.

CAARMS. With regards to FRS, the presence of one or more than one was not significantly associated with transition to FEP ($p = 0.388$ and $p = 0.109$, respectively). However, when taking into account each FRS individually, a statistical significant association was found between passivity experiences and later transition to psychosis ($p = 0.029$).

Early Functioning of Individuals at CHR and Experiencing FRS

Figure 2 shows the comparison of the mean scores between HVs and CHR individuals in the domains of the PAS. A third subgroup formed by those individuals at CHR who presented with FRS is also included.

There were statistically significant differences across the four domains – sociability and withdrawal ($p < 0.001$), peer relationships ($p < 0.001$), scholastic performance ($p = 0.002$), and adaptation to school ($p < 0.001$). CHR individuals disclosed lower levels of adjustment and functioning when they were children compared to HVs. In our sample, even poorer levels were reported among those CHR individuals with FRS. In fact, CHR individuals with FRS reported significantly poorer adjustment in the PAS total score ($p = 0.024$), specifically for peer relationships ($p = 0.024$) and scholastic performance ($p = 0.046$), than those at CHR but without FRS. However, no differences were found between individuals at CHR who had made transition to FEP 2 years later and those who did not.

Discussion

Our study, based on a sample of 60 help-seeking CHR individuals and 60 HVs, aimed to describe the prevalence of FRS among CHR individuals, their possible predictive value to future transition to psychosis and the early levels of adjustment and functioning among CHR individuals. More specifically, our findings were as follows: (1) the prevalence of at least one FRS among CHR individuals was over 43% and over 20% for more than one FRS, (2) among all FRS, only passivity experiences were associated with future transition to psychosis and (3) individuals at CHR presented significantly lower levels of functioning and adjustment during their childhood across educational, social and peer relationship domains, with those who reported FRS being even more affected. However, this did not predict future transition to psychosis.

FRS have been considered non-understandable psychological phenomena, non-culture dependent and, probably, the essence of schizophrenia [7, 22]. However, the diagnostic specificity of schneiderian FRS for schizophrenia has long been challenged, and a number of studies have called into question the continuous emphasis on bizarre delusions and special types of hallucinations (such as hearing voices conversing with one another or voices heard commenting on one's actions) in diagnostic classifications [23]. Indeed, FRS appear to be highly prevalent in the whole spectrum of functional psychotic disorders, including affective psychoses, where the prevalence of FRS has been reported to range between 22 and 29% [10, 11, 24]. Therefore, FRS may lack discriminatory diagnostic value among psychotic disorders [23].

Notably, we also found a high prevalence of FRS in young individuals at increased risk of developing psychosis. However, their presence was not indicative of conversion to psychotic disorders. With the exception of passivity phenomena, which were among the most prevalent FRS in our sample, none of the schneiderian FRS showed a clear association with potential transitions. This finding is in line with previous empirical phenomenological studies that have described the decreased and disturbed 'sense of self-presence' as a core feature in schizophrenia and its prodromal phase, involving different and vague self-perceptions such as depersonalization, somatic disturbances and feelings of identity loss [25, 26].

Overall, our results are in agreement with previous research supporting the view that FRS should be considered symptoms of psychosis rather than symptoms of schizo-

Psychopathology
DOI: 10.1159/000369859

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/18/2015 4:02:28 PM

© 2015 S. Karger AG, Basel. This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

phrenia [9, 11, 24]. However, the low transition rates and the fact that most CHR individuals suffered from mood and anxiety disorders suggest that FRS should not only be considered markers for psychotic disorders but also for a wider range of mental disorders, which may present with psychotic experiences that may not evolve to frank psychotic disorders [4, 27, 28].

These findings might support the dimensional phenotypic classification that is being proposed for schizophrenia. According to the neurodevelopmental model of schizophrenia, psychotic illness would be at the end of a spectrum of abnormal neurodevelopmental processes that begin years before the onset of illness [29]. These processes, resulting from different genetic [30], obstetric [31] and environmental factors [32], might not be specific predictors of schizophrenia alone but of a wide range of disorders and future clinical need [29]. Supporting the view of a neurodevelopmental perspective, our study showed that those individuals with poorer functioning and adjustment as children across educational, peer relationship and social domains might eventually develop psychotic symptoms as young adults, and that there was a dose-response relationship between poor premorbid adjustment and presence of FRS. Although not associated with later transition to full-blown psychosis in our sample, poor functioning and adjustment from early stages in development might be indicative of some vulnerability traits in these individuals to experience psychotic symptoms in the future, if they were not emerging already, as well as other non-psychotic mental health problems. It is unclear which aspects of poor functioning and adjustment in childhood might specifically predict one disorder over another. There is some evidence from longitudinal studies that certain receptive language, communication and cognitive deficits in childhood might specifically be associated with future psychosis [5, 33], whereas deficits in emotional and social/interpersonal development might be common predictors of psychosis, depression and bipolar and anxiety disorders [33]. Accordingly, poor premorbid adjustment might be the earliest manifestation of a common neurodevelopmental pathway for different psychiatric disorders and/or functional impairment [34–36]. Further understanding and early intervention at these stages might be helpful to prevent future negative outcomes.

Our study has several strengths. For example, it was controlled, including both HVs and help-seeking CHR individuals. Also, its longitudinal design and high retention rates over 2 years allowed us to address the limitations associated with cross-sectional studies. However, our results should be considered in the light of some limitations. Our sample size did not allow further adjustment for comorbid mental disorders, which may have shed light on specific associations between the level of impairment and increased risk for non-psychotic mental disorders. Studies with larger samples will also be required in order to replicate findings regarding associations between specific FRS and future conversions to psychosis, especially the relevance of those FRS that were absent in our sample (somatic hallucinations and delusional perceptions). Early premorbid adjustment was measured retrospectively, bringing the possibility of recall bias. Finally, as transitions to psychosis were described in a 2-year follow-up period, it is possible that conversion rates could have been higher if follow-up had been longer.

Acknowledgements

This work was supported by the National Institute for Health Research (NIHR) – programme grant RP-PG-0606-1335 'Understanding Causes and Developing Effective Interventions for Schizophrenia and Other Psychoses' (awarded to P.B.J.). The work forms part of the NIHR Collaboration for Leadership in Applied Health Research and Care for Cambridgeshire and Peterborough (CLAHRC-CP). The NIHR had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, and the decision to submit the paper for publication.

The authors thank the PAATH Study team (Michelle Painter, Gillian Shelley, Chris McAlinden, Carolyn Crane, and Gerhard Smith) and all members of CAMEO services for their help and support in the execution of this study.

Disclosure Statement

The authors have no conflicts of interest based on business relationships of their own or of immediate family members.

References

1 Hui C, Morcillo C, Russo DA, Stochl J, Shelley GF, Painter M, Jones PB, Perez J: Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. Schizophr Res 2013;148:175–180.

2 Salokangas RK, Ruhrmann S, von Reventlow HG, Heinimaa M, Svirskis T, From T, Luutonen S, Juckel G, Linszen D, Dingemans P, Birchwood M, Patterson P, Schultze-Lutter F, Klosterkotter J: Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophr Res 2012;138:192–197.

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/18/2015 4:02:28 PM

3 Correll CU, Hauser M, Auther AM, Cornblatt BA: Research in people with psychosis risk syndrome: a review of the current evidence and future directions. J Child Psychol Psychiatry 2010;51:390–431.
4 Armando M, Nelson B, Yung AR, Saba R, Monducci E, Dario C, Righetti V, Birchwood M, Fiori NP, Girardi P: Psychotic experience subtypes, poor mental health status and help-seeking behaviour in a community sample of young adults. Early Interv Psychiatry 2012;6: 300–308.
5 Bearden CE, Wu KN, Caplan R, Cannon TD: Thought disorder and communication deviance as predictors of outcome in youth at clinical high risk for psychosis. J Am Acad Child Adolesc Psychiatry 2011;50:669–680.
6 Smeets F, Lataster T, van WR, de GR, Ten HM, Van OJ: Testing the hypothesis that psychotic illness begins when subthreshold hallucinations combine with delusional ideation. Acta Psychiatr Scand 2013;127:34–47.
7 Schneider K: Clinical Psychopathology. New York, Grune & Stratton, 1959.
8 Carpenter WT Jr, Strauss JS: Cross-cultural evaluation of Schneider's first-rank symptoms of schizophrenia: a report from the International Pilot Study of Schizophrenia. Am J Psychiatry 1974;131:682–687.
9 Rosen C, Grossman LS, Harrow M, Bonner-Jackson A, Faull R: Diagnostic and prognostic significance of Schneiderian first-rank symptoms: a 20-year longitudinal study of schizophrenia and bipolar disorder. Compr Psychiatry 2011;52:126–131.
10 Peralta V, Cuesta MJ: Diagnostic significance of Schneider's first-rank symptoms in schizophrenia. Comparative study between schizophrenic and non-schizophrenic psychotic disorders. Br J Psychiatry 1999;174: 243–248.
11 Ihara K, Morgan C, Fearon P, Dazzan P, Demjaha A, Lloyd T, Kirkbride JB, Hayhurst H, Murray RM, Jones PB: The prevalence, diagnostic significance and demographic characteristics of Schneiderian first-rank symptoms in an epidemiological sample of first-episode psychoses. Psychopathology 2009;42: 81–91.
12 Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L: First-episode schizophrenia. II. Premorbid patterns by gender. Schizophr Bull 1996;22:257–269.
13 Addington J, Addington D: Patterns of premorbid functioning in first episode psychosis: relationship to 2-year outcome. Acta Psychiatr Scand 2005;112:40–46.
14 Addington J, Penn D, Woods SW, Addington D, Perkins DO: Social functioning in individuals at clinical high risk for psychosis. Schizophr Res 2008;99:119–124.
15 Grano N, Karjalainen M, Suominen K, Roine M: Poor functioning ability is associated with high risk of developing psychosis in adolescents. Nord J Psychiatry 2011;65:16–21.
16 Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J: Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust NZ J Psychiatry 2005;39:964–971.
17 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(suppl 20):22–33.
18 Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276.
19 Larsen TK, Friis S, Haahr U, Johannessen JO, Melle I, Opjordsmoen S, Rund BR, Simonsen E, Vaglum PV, McGlashan TH: Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. Br J Psychiatry 2004;185:108–115.
20 R Development Core Team: R: A language and environment for statistical computing. Vienna, R Foundation for Statistical Computing, 2014.
21 Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR: What does the PANSS mean? Schizophr Res 2005;79:231–238.
22 Jaspers K: Clinical Psychopathology. Chicago, University of Chicago, 1963.
23 Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, Malaspina D, Owen MJ, Schultz S, Tsuang M, Van OJ, Carpenter W: Definition and description of schizophrenia in the DSM-5. Schizophr Res 2013;150:3–10.
24 Nordgaard J, Arnfred SM, Handest P, Parnas J: The diagnostic status of first-rank symptoms. Schizophr Bull 2008;34:137–154.
25 Moller P, Husby R: The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. Schizophr Bull 2000;26:217–232.
26 Parnas J, Handest P, Saebye D, Jansson L: Anomalies of subjective experience in schizophrenia and psychotic bipolar illness. Acta Psychiatr Scand 2003;108:126–133.
27 Van OJ, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L: A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol Med 2009;39:179–195.
28 Yung AR, Nelson B, Baker K, Buckby JA, Baksheev G, Cosgrave EM: Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. Aust NZ J Psychiatry 2009;43:118–128.
29 Rapoport JL, Giedd JN, Gogtay N: Neurodevelopmental model of schizophrenia: update 2012. Mol Psychiatry 2012;17:1228–1238.
30 Raznahan A, Greenstein D, Lee Y, Long R, Clasen L, Gochman P, Addington A, Giedd JN, Rapoport JL, Gogtay N: Catechol-*o*-methyl transferase (COMT) val^{158}met polymorphism and adolescent cortical development in patients with childhood-onset schizophrenia, their non-psychotic siblings, and healthy controls. Neuroimage 2011;57: 1517–1523.
31 Clarke MC, Tanskanen A, Huttunen M, Leon DA, Murray RM, Jones PB, Cannon M: Increased risk of schizophrenia from additive interaction between infant motor developmental delay and obstetric complications: evidence from a population-based longitudinal study. Am J Psychiatry 2011;168:1295–1302.
32 Van OJ, Kenis G, Rutten BP: The environment and schizophrenia. Nature 2010;468: 203–212.
33 Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, Poulton R: Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch Gen Psychiatry 2002;59: 449–456.
34 Carrion RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, Correll CU, Cornblatt BA: Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry 2013;70:1133–1142.
35 Carrion RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, Cornblatt BA: Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. Am J Psychiatry 2011;168:806–813.
36 Salokangas RK, Heinimaa M, From T, Löyttyniemi E, Ilonen T, Luutonen S, Hietala J, Svirskis T, von Reventlow HG, Juckel G, Linszen D, Dingemans P, Birchwood M, Patterson P, Schultze-Lutter F, Ruhrmann S, Klosterkötter J; EPOS group: Short-term functional outcome and premorbid adjustment in clinical high-risk patients. Results of the EPOS project. Eur Psychiatry 2014;29: 371–380.

Downloaded by:
Royal Free London Foundation Trust
194.176.105.141 - 2/18/2015 4:02:28 PM

© 2015 S. Karger AG, Basel. This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

Appendix 13 Insights from the clinical team

Observations concerning our high-risk cohort

To ensure the reliability of the CAARMS scores, each assessment was discussed at length by the research team in an inter-rater reliability meeting, scored individually and recorded before a consensus was reached. The identity of each case was anonymised to eliminate bias.

The identification of HR for the purposes of the LEGS trial and the PAATH study was decided at the inter-rater reliability meeting. This process of assessment provided consistent symptom ratings and therefore reliable decisions over the period of the study. As knowledge, experience and understanding grew, this also greatly contributed to both the clinical team's and the research team's understanding of the complexity of psychotic symptoms.

Clinical and consensus decisions were discussed with the research consultant psychiatrist and trial co-ordinator (consultant psychologist) at a pre-(CAMEO) clinical meeting. There were many instances when a score was 'over threshold', that is, psychotic according to the CAARMS algorithm, but the general presentation did not necessarily fit with the CAMEO clinical team's criteria for inclusion on its caseload and continued care. However, the CAARMS scores, detailed feedback and clinical discussions all contributed positively to enhancing the decision-making within the CAMEO clinical team meetings. The extended assessments improved both the research team's and the clinical team's knowledge and understanding of the relationship between psychotic symptoms and disorders and the accurate identification of a first episode of psychosis. The CAMEO team have continued to use the CAARMS as part of the assessment process as it has proved to be a useful tool in understanding the intensity, frequency and level of distress of symptoms.

The young people seen during the research presented to their GP or another professional with symptoms that indicated the early stages of a psychotic illness. It became apparent that this is a complex group. The psychotic symptoms were often comorbid with depression, anxiety, obsessive–compulsive disorder or traits of a variety of personality disorders.

These patients tended to be very impaired by their symptoms as identified (as determined in *Appendix 7*). It was common to find that they were not achieving their potential generally and that they struggled in their relationships with others. Many of the young people who we assessed continue to suffer negative symptoms. They continue to have extremely poor social networks and may become (or remain) dependent, both financially and emotionally, on their parents or partners. They may be underachieving academically or in their careers because of the mental health difficulties that they experience. It was also evident that they had a higher than average risk of suicide or self-harming behaviours.

One of the most worrying aspects of this troubled group of patients is that very often they do not engage well with offers of support from adult mental health services.

Participants presented with a degree of subthreshold psychotic symptoms, which complicated their general mental health presentation. This caused complications for them at the beginning of their pathway into care because their presenting symptoms did not easily fit into the available adolescent or adult mental health services.

Participants described a variety of symptoms and were not a homogeneous group. It was rarely clear, from one interview, what the diagnosis was. Although they did not meet criteria for a psychotic illness, many young people had subthreshold symptoms for psychosis that could range from infrequent but frightening auditory and visual hallucinations to paralysing social anxiety or moderate levels of paranoia.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Common problems included loss of concentration, sleep difficulties and increasing social isolation. Notably, all of these symptoms are present in other mental health disorders or are characteristics of young people at a difficult stage of their lives.

The assessments were potentially therapeutic in themselves. The more detailed second assessment session allowed for more trust to be built up and often resulted in further disclosure of symptoms; it certainly led to a better understanding of symptoms. This may have been because the CAARMS assessments were usually conducted on a one-to-one basis and in most cases with a familiar clinician. This allowed for an improved 'alliance' between the young person and the interviewer during the CAARMS assessment. This second detailed interview reassured participants that they were being taken seriously and that their experience was being validated by a professional.

More often than not, those assessed as having subthreshold symptoms of psychosis required some psychological therapy. Referring a young person with psychotic symptoms on to psychological services was sometimes problematic. The majority of services located within primary care were not resourced to deal with young people who have psychotic symptoms as part of their presenting problems. The secondary mental health services that do work with people experiencing hallucinations or delusions were completely overwhelmed and were unable to spend the time on engagement that this group of patients requires. This resulted in patients not being seen or followed up by the secondary services. It was challenging to address the issue of where to treat this group of patients while considering putting their best interests first.

For the first part of the trial, the CAMEO team agreed that those who crossed the threshold on CAARMS should have an extended assessment period to consider their differential diagnosis and clinical needs. More often than not these patients were discharged to their GP after a period of 3–6 months having benefited from the enhanced treatment within an EIS. Subsequently, as changes within the mental health trust necessitated stricter criteria, people with psychotic symptoms over the threshold for psychosis on the CAARMS but not a suspected psychotic disorder were referred to another secondary or primary care team for treatment of another primary disorder. Therefore, they did not receive this specialist care.

As a group of professionals who have monitored young people with HR symptoms for at least 5 years, we would contend that this patient group represents an unmet need within mental health services. We could be preventing some young people from ever crossing that threshold into full-blown psychosis, enabling them to escape the hugely debilitating, costly and distressing experience of having a psychotic illness. Furthermore, we could be intervening, giving age-appropriate psychoeducation, treatment and support to all those who may never cross that threshold and who just simply carry on experiencing a subthreshold level of psychotic symptoms. This HR group of patients, mostly aged between 16 and 25 years, were at a crucial time in their lives. We have observed that they need as much help and support as those who are more unwell and who fit more neatly into the traditional psychiatric diagnoses.

Critique of the Comprehensive Assessment of At-Risk Mental States

Conviction about beliefs

Assessing the level of conviction about a belief is central to establishing where on the spectrum of psychosis the symptoms lie. Rating the percentage of conviction, both at the time of experiencing the thought and afterwards, would help to clarify this.

If someone is suffering from social anxiety, they may have total conviction that people are talking about them. In this case it is the oddness or unusualness of the belief in context that is important to understand, although this is complex when many delusional ideas have some basis in reality anyway.

Insight

It is always important to assess level of insight into the unusual thought or belief. Insight can range from someone knowing that they are thinking erroneously but not being able to stop to not being able to even consider any alternative explanation. This seems to significantly vary naturally in people, depending on resourcefulness and intelligence. Conversely, concrete thinking can lead to rather fixed beliefs.

Unusual thought content

There was a strong tendency for individuals to answer the question at the beginning of the CAARMS, 'Have you felt that something odd is going on that you can't explain?', with a description of all of the symptoms that distress them most. This can distract from the process and almost never elicited delusional mood.

The manner in which the questions are worded allows misinterpretation of the answers about delusional mood. Many people answer this by describing symptoms of derealisation, for example that they feel separate from the world, as if they are in a bubble. Some people experience significant derealisation or dissociation as a result of anxiety or trauma that arguably should score higher on the CAARMS (as a perceptual abnormality) than a '3', that is, low-level symptoms and the severity properly assessed. A better example could also be associated with these phenomena.

Others express that they feel that the world is going to end or that something bad is going to happen and have felt that for years. Delusional mood, however, apart from being rare, is a time-limited precursor to a delusion. It is a self-referential alienation from the environment, for example that everything is 'set up for you like you're in a theatre', as opposed to the detachment of the emotional component from the perception or 'as if it's a stage set'.

Non-bizarre ideas

Paranoia is difficult to assess as it is possible to have extreme fixed beliefs around others wishing you harm without having any delusional explanation of the scenario.

The CAARMS does not fully explore the person's belief system around the paranoid thinking. Identifying (1) whether or not there is a wider delusional system into which the paranoid thought fits and (2) whether the person believes that he or she is the sole target or if everyone around him or her is also suffering the same problems helps rate more accurately the extent of the delusional belief.

It is necessary to establish the context of the belief to determine whether or not it is triggered by a real situation. If someone thinks that there are people out to get him or her, he or she may be part of a violent or criminal social network in reality.

It is quite common to find people who have a single unusual belief about themselves that may relate to another mental health diagnosis, such as body dysmorphic disorder. The question of whether or not dysmorphia is delusional is contentious.

Obsessional thinking and beliefs can seem very much like delusions and are not clearly differentiated on the CAARMS. People with these beliefs can normally retain some understanding that their thoughts are odd. Enquiring about other obsessional aspects of the person's presentation will aid understanding of this.

Perceptual abnormalities

The most frequent reason why participants crossed the threshold on the CAARMS was that perceptual abnormalities reached the threshold for psychosis for more than a week. If this was the only symptom, often the clinical team did not regard these participants as having a first episode of psychosis. This created an important dilemma as they were also over the threshold for not 'HR' according to the CAARMS and therefore did not meet the PAATH study criteria.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Hallucinations can also be related to a disturbance of mood or trauma, an indicator of a schizotypal presentation or emotional instability. The presence of hallucinations with no other psychotic symptoms may be an indicator that the person is not primarily suffering a psychotic illness. For these reasons it is useful to assess the possible comorbidity of other disorders that can include the experience of psychotic or psychotic-like symptoms such as trauma, post-traumatic stress disorder, social anxiety, depression, obsessive–compulsive disease or various personality traits.

Understanding the origin of the voice experienced is important:

- Does it sound like the person's own thoughts?
- Might it be their own thoughts?
- Are they attributed to someone else?
- Do they know who the voice belongs to?
- Is the voice heard internally or in external space?

Assessing the level of distress that perceptual abnormalities elicit is crucial. Some people are not distressed by hearing voices and it can be a positive protective experience.

The perceptual abnormalities scale does not adequately describe the difference between subthreshold and threshold for psychosis. For example, where on the scale can you rate a shouting voice that cannot be understood but which is distressing? Or a vague outline of a male figure jumping towards the person with claw hands? Another point on the scale below threshold would resolve this dilemma.

Disorganised speech

We assessed only a very few people with recognisable disorganised speech. It was characterised generally by 'flight of ideas', 'pressure of speech', tangentiality and only very rarely by poverty of speech, all of which could be possible indicators of thought disorder.

We believe that disorganised speech symptoms are not adequately covered in the CAARMS, especially as the severity of the CAARMS disorganised speech component is the strongest predictor of transition to frank psychosis. Of those we assessed with these observable symptoms, the majority went on to be diagnosed with psychosis.

Much time can be spent discussing someone's slight subjective communication difficulties and there is a case for scoring only what can be seen objectively: mild disconnected speech.

Risk

Because the rating of suicidality and self-harm is combined, it makes a true assessment of the level of risk to self very difficult to determine. The two behaviours should be rated separately to provide any meaningful indication of risk.

Duration of symptoms

There is a group of people, mostly with a range of personality traits including schizotypy, who have suffered from symptoms since childhood or early adolescence, especially hallucinations but also persistent overvalued ideas. In our experience these people are not at risk of becoming delusional or of having a psychotic disorder as their beliefs and experiences have been stable for a long period.

Applying the parameters that (1) the symptoms under assessment should have been present for < 5 years or (2) there is evidence of the symptoms worsening would help avoid labelling someone as psychotic when he or she has another primary problem.

Other psychotic-like symptoms

Dissociation as a result of anxiety or trauma can cause significant distress; arguably it could score on the CAARMS.

The criteria for BLIPS are problematic. Florid psychotic symptoms, especially if the picture is not complicated by drug use or an organic presentation that resolves within a week, were rare.

Cultural context

Asking questions to find out whether a patient's relatives or friends might feel the same can eliminate the misidentification of paranoid or delusional thinking. We experienced the following scenarios:

- Families having cultural beliefs around seeing ghosts or spirits that can influence a person's explanation of his or her experiences.
- Individuals were part of a social group in which violence and harassment were common.
- Religious beliefs caused difficulties when assessing whether or not someone had a delusional belief, in particular cross-cultural misinterpretations of someone's belief system.

The CAARMS does refer to these issues in the 'Guidelines for rating' but there should be a prompt within the individual sections for this.

Level of symptoms

There is no evidence, from our experience or from the literature, to support the possibility that mild symptoms, however often they are experienced, are associated with a risk of psychosis. Therefore, we suggest excluding on all of the scales the lowest level of possible 'at-risk' symptoms (i.e. level 3).

Global Assessment of Functioning

The GAF is included in the CAARMS to establish the level of functioning in relation to the 'trait plus state' criteria. It would be helpful to include prompting questions to elicit this information, especially with respect to mood, anxiety and work.

Conclusion

As the brief version of the CAARMS focuses on particular symptoms, it does not cover the wider clinical picture and this is an issue that needs to be considered when deciding whether someone has a psychotic illness or attenuated psychotic symptoms.

If the use of the CAARMS is preceded by a good knowledge of symptomatology and there is an assumption of clinical skills being used in the assessment process, there is less need for detail and explanation. However, its use by research assistants in RCTs will inevitably lead to inaccuracies.

The CAARMS provides a useful backbone for assessing psychotic symptoms. Its limitations as a tool are mostly concerned with the complexity of the symptoms to be assessed and the current lack of understanding of who is at risk of developing psychosis.

To understand this group of patients, assessing who makes a 'transition' to psychosis may be the wrong question. Is it not better to ask what these people suffer from and what happens to them over time? Do they primarily have a depressive or anxiety-related illness?

In our experience, using the CAARMS to assess attenuated symptoms has not led to a greater understanding of who is prodromal for psychosis.

It would be beneficial to use a wider system for training and concordance to ensure accurate use. We had to develop our own guidelines for consistent use internally.

© Queen's Printer and Controller of HMSO 2016. This work was produced by Perez *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

For future research we consider that two baseline CAARMS, a month apart and before consent, would go some way to eliminating 'false' transitions, for example if someone disclosed a symptom the second time that CAARMS questions were asked which was not newly experienced. Establishing a rapport may take more than one session. On many occasions, at the second meeting, people disclosed further symptoms, having established trust and having the knowledge that they were being taken seriously.

It is important not to lose track of the point – that ideally we would predict who is prodromal rather than who has psychotic-like symptoms.

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

Published by the NIHR Journals Library